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(54) Title: METHOD FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH APOPTOSIS USING N–HETEROCYCLIC GLYOXYLAMIDE COMPOUNDS

(57) Abstract

A method of composition is disclosed for the treatment of disorders associated with apoptosis using N–heterocyclic glyoxylamide compounds. The heterocycles are indole–3–yl or indolizin–1–yl.

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Description

METHOD FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH APOPTOSIS USING N-HETEROCYCLIC GLYOXYLAMIDE COMPOUNDS

This invention relates to a method for the treatment of disorders associated with apoptosis using N-heterocyclic glyoxylamide compounds, a use of N-heterocyclic glyoxylamide compounds for the treatment of disorders associated with apoptosis and a composition for the treatment of disorders associated with apoptosis comprising N-heterocyclic glyoxylamide compounds.

BACKGROUND OF THE INVENTION

In multicellular organisms, homeostasis is maintained through a balance between cell proliferation and cell death. Cell death is roughly classified into necrosis and apoptosis. Apoptosis is observed in a physiological ontogeny, or an appearance of disorders or pharmaceutics effects, and it has been thought to occur on the basis of activation of the nature program in individual cell, which differs from necrosis. Apoptosis and necrosis are different from each other in terms of that apoptosis is associated with RNA synthesis and protein synthesis, while necrosis is not.

Although apoptosis-inducing stimulus and the mechanism thereof are various, its morphologic features are common. The first morphologic change is a formation of condensation of chromatin, which is almost associated

with DNA fragmentation. Then the condensation is observed, it appears that the compaction of cytoplasm occurs, and cell itself forms cell fragments called apoptotic bodies. The formed apoptotic bodies are quickly phagocytosed and disintegrated by adjacent cells or macrophages, and the like so as to lead apoptosis.

Brain Research 693 (1995) 101-111 and THE JOURNAL BIOLOGICAL CHEMISTRY Vol. 271, No.51, (1996) 32722-32728 disclose that secretory phospholipase A2 (sPLA2) has neurotoxicity, but it does not disclose that the neurotoxicity therein is associated with apoptosis. Brain Research 651 (1994) 353-356 discloses that group II PLA2 is expressed in rat brain after severe forebrain ischemia, but it does not disclose any relationship between group II PLA2 and neuronal death. Brain Research 752 (1997) 203-208 discloses that a phospolipase A2 innibitor, quinacrine, reduces infarct size in rats after transient middle cerebral artery occlusion, but it does not disclose that the infarction therein is associated with apoptosis. WO 96/40982 discloses that a PLA2 inhibitor is useful in the treatment of neurodegenerative diseases, but it does not disclose that a secretory PLA2 inhibitor such as compounds used in the present invention can be used to treat such diseases . USP 5478857 discloses that a PLA2 inhibitor is useful in the treatment of Alzheimer's diseases, but it does not disclose that a secretory PLA2 inhibitor such as compounds used in the present invention can be used to treat such diseases.

SUMMARY OF THE INVENTION

It is an object of this invention to provide a method of treatment of a mammal, including a human, currently afflicted with disorders assiciated with apoptosis, said method comprising administering to said mammal a therapeutically effective amount of an N-heterocyclic glyoxylamide compound.

It is also an object of this invention to use an N-heterocyclic glyoxylamide compound for the manufacture of a medicament for treatment of a mammal, including a human, currently afflicted with disorders associated with apoptosis.

It is also an object of this invention to provide a composition for treatment of disorders associated with apoptosis, said composition comprising a therapeutically effective amount of an N-heterocyclic glyoxylamide compound.

The present invention is considered to be useful for disorders associated with apoptosis, in more detail, chronic deseases such as Alzheimer's desease, a number of scleroma, ataxia, talangiectasia, prion-induced neuronal cell death, and the like, or acute diseases such as stroke, and the like.

TREATMENT METHODS

General Aspects of the Method:

It will be apparent to those skilled in the art that a compound of the present invention can be co-administered with other therapeutic or prophylactic agents and/or medicaments that are not medically incompatible therewith.

The regimen for treatment may stretch over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to three oral doses per day, each from about 0.01 to about 50 mg/kg of body weight are used with preferred doses being from about 0.04 to about 5.0 mg/kg.

The specific dose of N-heterocyclic glyoxylamide compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, the size and age of the patient, the severity of disorders associated with apoptosis, and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Method of administration.

The N-heterocyclic glyoxylamide compounds are most often used in the method of the invention in the form of pharmaceutical formulation, as described infra. Other forms of administration may be used in both human and veterinary contexts. Such alternative forms include the use of suppositories, transderm patches, and compositions

for buccal or nasal administration, for example lozenges, nose drops, an aerosol spray, or transdermal patch.

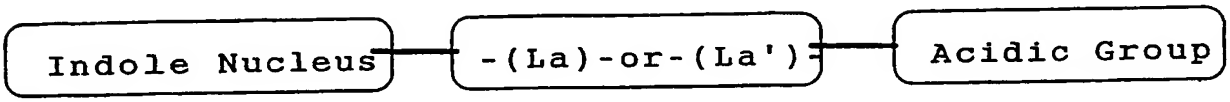
COMPOUNDS USED IN TREATMENT METHOD OF THE DISORDERS ASSOCIATED WITH APOPTOSIS

The method for treating subjects for the occurrence or prevention of disorders associated with apoptosis comprises administering an effective amount of an N-heterocyclic glyoxylamide compound. Suitable 1H-indole-3-glyoxylamide compounds for the practice of the method of treating and preventing disorders associated with apoptosis as taught herein are those described in European Patent Application No. 95302166.4, Publication No. 0 675 110 (publ., 4 October 1995). Suitable 1H-indole-3-glyoxylamide compounds are also those disclosed in United States patent application No 08/469,954 filed 6 June 1995, the disclosure of which is incorporated herein by reference. Formulations containing these 1H-indole-3-glyoxylamide compounds and methods of making them are also fully described in European Patent Office Publication European Patent Application No. 95302166.4 and United States patent application No 08/469,954. Suitable indolizine compounds are disclosed in WO 9603383 (Publ., 8 February 1996).

Definitions:

The words, "acid linker" refers to a divalent linking group symbolized as, -(L_a)- or (La')-, which has the function of joining the 4 or 5 position of the

indole nucleus or the 7 or 8 position of the indolizine nucleus to an acidic group in the general relationship:



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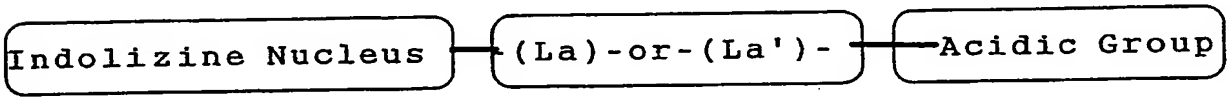
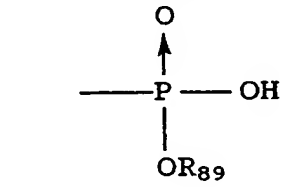


The words, "acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group -(La)- or (La')- that connects the 4 or 5 position of the indole nucleus or the 7 or 8 position of the indolizine nucleus with the acidic group.

The word "acidic group" is selected from

-5-tetrazolyl,

$-SO_3H$,



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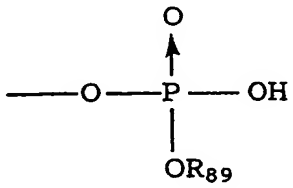

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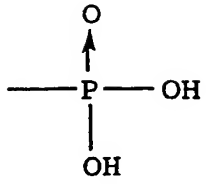

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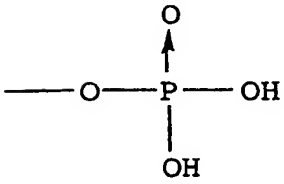

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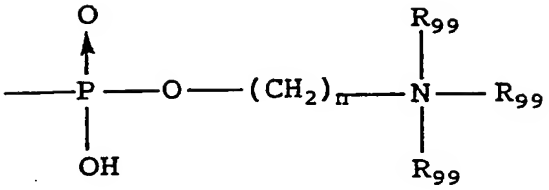

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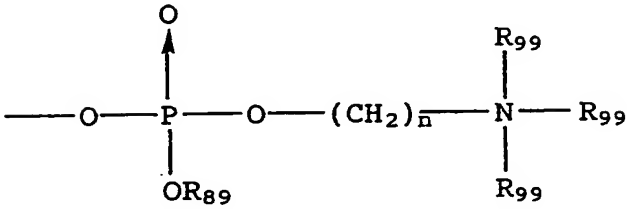

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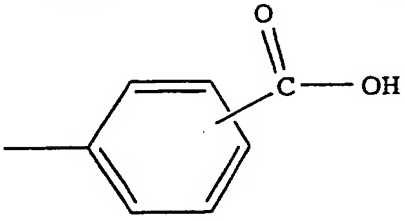

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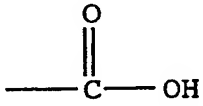

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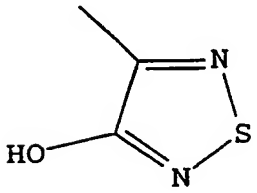
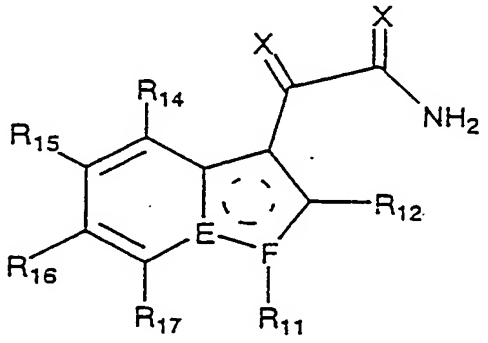


;

where n is 1 or 8., R89 is a metal or C1-C10 alkyl, and R99 is hydrogen or C1-C10 alkyl.

Preferred compounds for use in the method or composition of the invention are those having the general formula (I) or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;



(I)

wherein ;

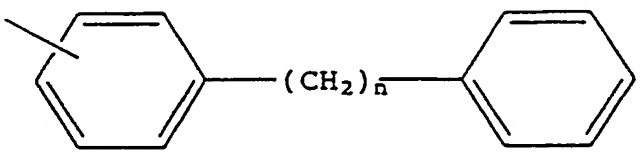
E and F are differently C or N;

---- is presence or absence of a double bond;

each X is independently oxygen or sulfur;

R_{11} is selected from groups (a), (b) and (c) where;

(a) is C_7-C_{20} alkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl; or carbocyclic radical selected from the group cycloalkyl, cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),

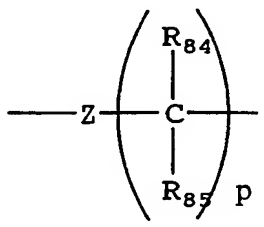


(bb)

where n is a number from 1 to 8; or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8;

(c) is the group -(L_1)-R_{81}; where, -(L_1)- is a divalent linking group having the formula;



where,

R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, carbolxy, carbalkoxy, or halo;

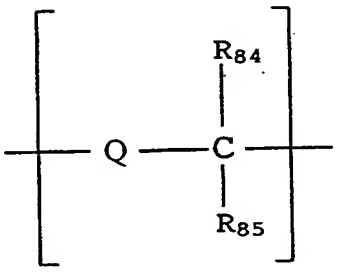
p is 1 to 5,

Z is a bond, -(CH_2)-, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

where R_{81} is a group selected from (a) or (b);

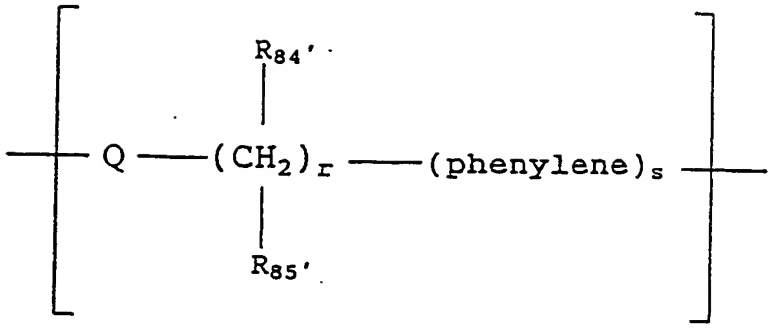
R_{12} is hydrogen, halo, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_3-C_4 cycloalkenyl, -O-(C_1-C_2 alkyl), or -S-(C_1-C_2 alkyl);

R_{14} is hydrogen or a group, -(L_a)-(acidic group) wherein -(L_a)- is represented by the formula;



where Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, and halo;

R_{15} is hydrogen or a group, -(L_a')-(acidic group) wherein -(L_a')- is represented by the formula;



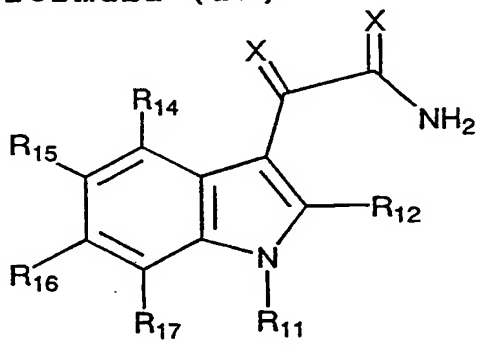
where r is a number from 1 to 7, s is 0 or 1, and Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84}' and R_{85}' are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, carboxy, carbalkoxy, and halo; provided that at least one of R14 or R15 must be the group, -(La)-(acidic group) or -(La')-(acidic group);

R_{16} is hydrogen, carboxyl or ester thereof;

R_{17} is selected from hydrogen, non-interfering substituents, selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_2-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -(CH_2)n-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO,

amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8.

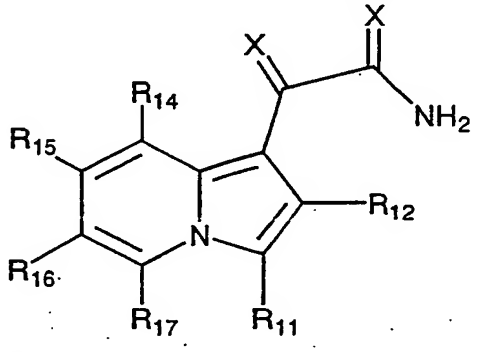
A preferred class of compounds for the method or composition of the invention are compounds represented by the formula (II):



(II)

wherein X, R11, R12, R14, R15, R16 and R17 are as defined above.

An alternatively preferred class of compounds for the method or composition of the invention are compounds represented by the formula (III):



(III)

wherein X, R11, R12, R14, R15, R16 and R17 are as defined above.

A further preferred class of compounds for the method or composition of the invention are the compounds represented by the formula (II) or (III) where both X's are oxygen, only one of R_{14} or R_{15} is -(L_a)-(acidic group) or -(La')-(acidic group), and the acidic group is carboxyl.

Specific preferred compounds and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof which are useful in the method or composition of the invention include the following:

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(B) dl-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]propanoic acid,

(C) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(E) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-4-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(F) [[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(G) [[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(L) [[3-(2-amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-propyl-1H-indol-4-yl]oxy]acetic acid,

(M) [[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(N) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-cyclopropyl-1H-indol-4-yl]oxy]acetic acid,

(O) 4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,

(P) mixtures of (A) through (O) in any combination,

(Q) (8-(Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(R) (3-Benzyl-8-(carbethoxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(S) (8-(Carbethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(T) (3-Benzyl-8-(carbethoxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(U) (8-(Carbethoxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(V) (8-Carbethoxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(W) (3-Benzyl-8-(t-butoxycarbonylmethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(X) (8-(Carbmethoxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(Y) (8-(Carbmethoxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(Z) (3-Benzyl-8-(carboxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-

phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(BB) (3-Benzyl-8-(carboxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(CC) (8-(Carboxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(DD) (8-(Carboxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(EE) (8-Carboxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(FF) (8-(Carboxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(GG) mixtures of (Q) through (FF) in any combination,

(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(JJ) [[3-(2-Amino-1,2-dioxoethyl)-6-ethoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(KK) [[3-(2-Amino-1,2-dioxoethyl)-6-n-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(LL) [[3-(2-Amino-1,2-dioxoethyl)-6-i-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(MM) [[3-(2-Amino-1,2-dioxoethyl)-6-cyclopropyloxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(NN) mixtures of (HH) through (MM) in any combination.

Most preferred in the practice of the method or composition of the invention include the following:

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Similarly, Most preferred in the practice of the method or composition of the invention include the following:

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid.

Similarly, Most preferred in the practice of the method or composition of the invention include the following:

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

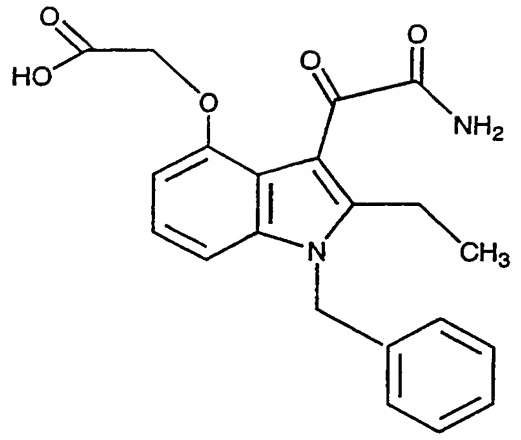
(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide.

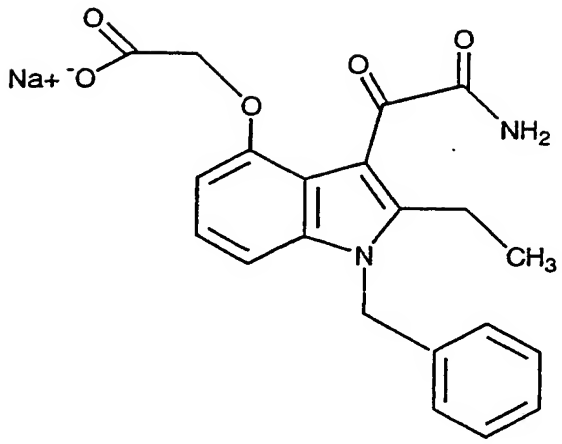
Similarly, Most preferred in the practice of the method or composition of the invention include the following:

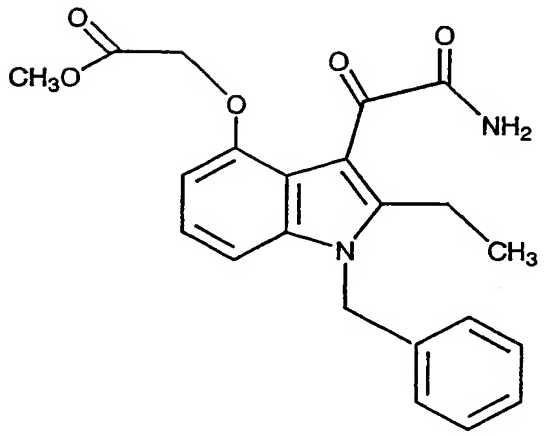
(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

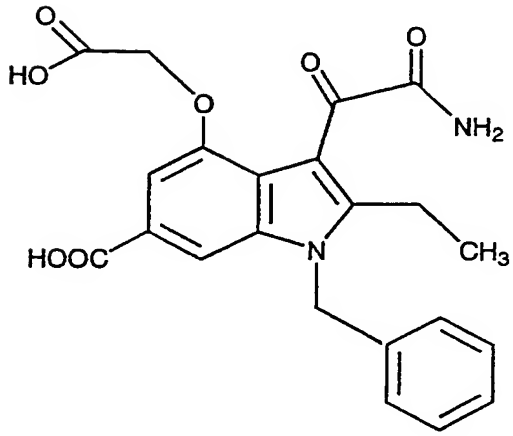
(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid.

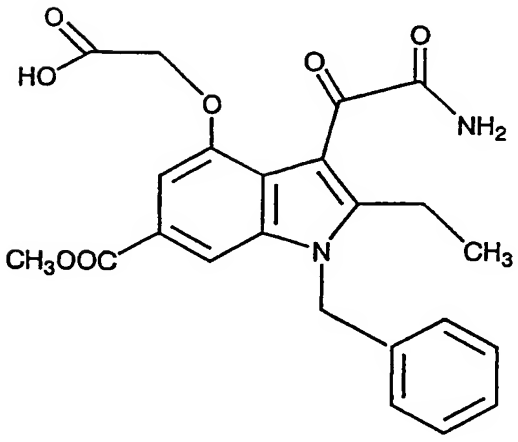
Most preferred in the practice of the method or composition of the invention are 1H-indole-3-glyoxylamides selected from the formula:



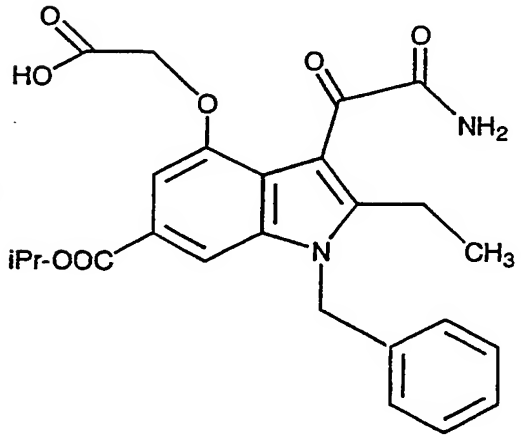




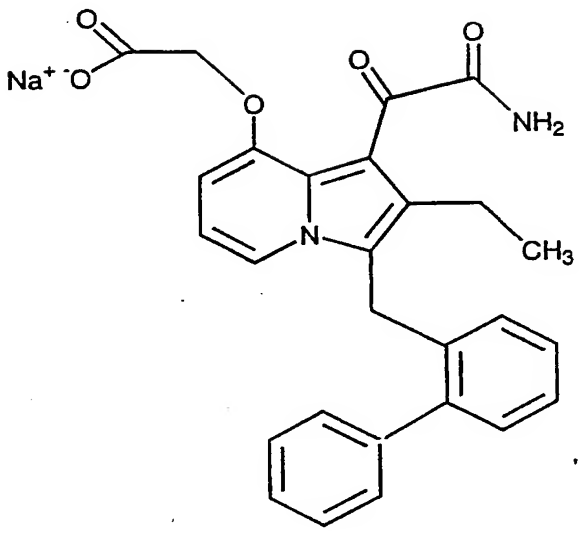


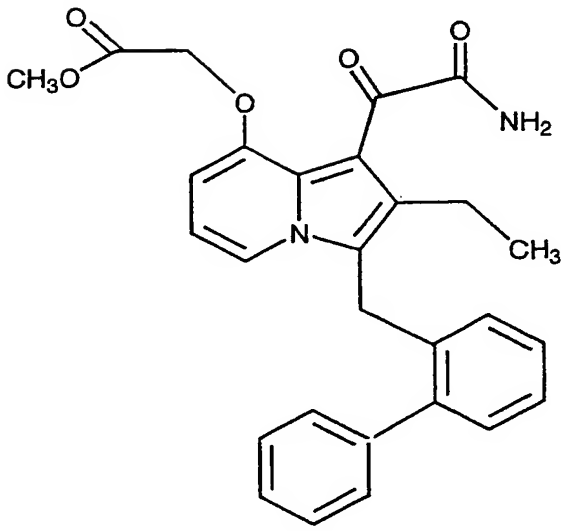


or

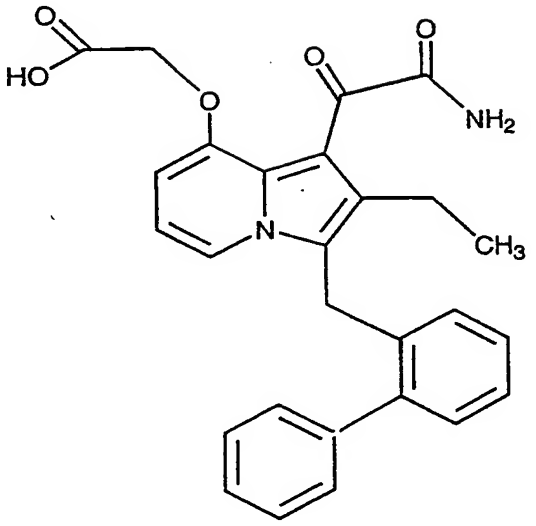


or indolizine-1-glyoxylamides selected from the formula:





or



The salts of the above 1H-indole-3-glyoxylamide compounds represented by formula (II) and named compounds (A) through (P), (HH) through (NN) and of indolizine-1-glyoxylamide compounds represented by the formula (III) and named compounds (Q) through (GG) are particularly useful in the method of the invention. In those instances where the 1H-indole-3-glyoxylamide compounds and indolizine-1-glyoxylamide compounds possess acidic or basic functional groups various salts may be formed which

are more water soluble and physiologically suitable than the parent compounds. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of the 1H-indole-3-glyoxylamide compounds and indolizine-1-glyoxylamide compounds used in the method or composition of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, basic group(s) present in the 1H-indole-3-glyoxylamide compound may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, bromide, chloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate,

mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain 1H-indole-3-glyoxylamide compounds and indolizine-1-glyoxylamide compounds may possess one or more chiral centers and may thus exist in optically active forms. Likewise, R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated for use by the method or composition of this invention.

Prodrugs are derivatives of the 1H-indole-3-glyoxylamide compounds or indolizine-1-glyoxylamide compounds which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the 1H-indole-3-glyoxylamide compounds and indolizine-1-glyoxylamide compounds have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters

(e.g., methyl or ethyl esters) derived from acidic groups (e.g., carboxyl) pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters.

The method of the invention can be practiced using pharmaceutical formulations containing compounds of the invention administered through the skin by an appliance such as a transdermal patch, as described in US Patents No. 5,296,222 and 5,271,940, the disclosures of which are incorporated herein by reference. Lipophilic prodrug derivatives of the compounds for formula II are particularly well suited for transdermal absorption administration and delivery systems.

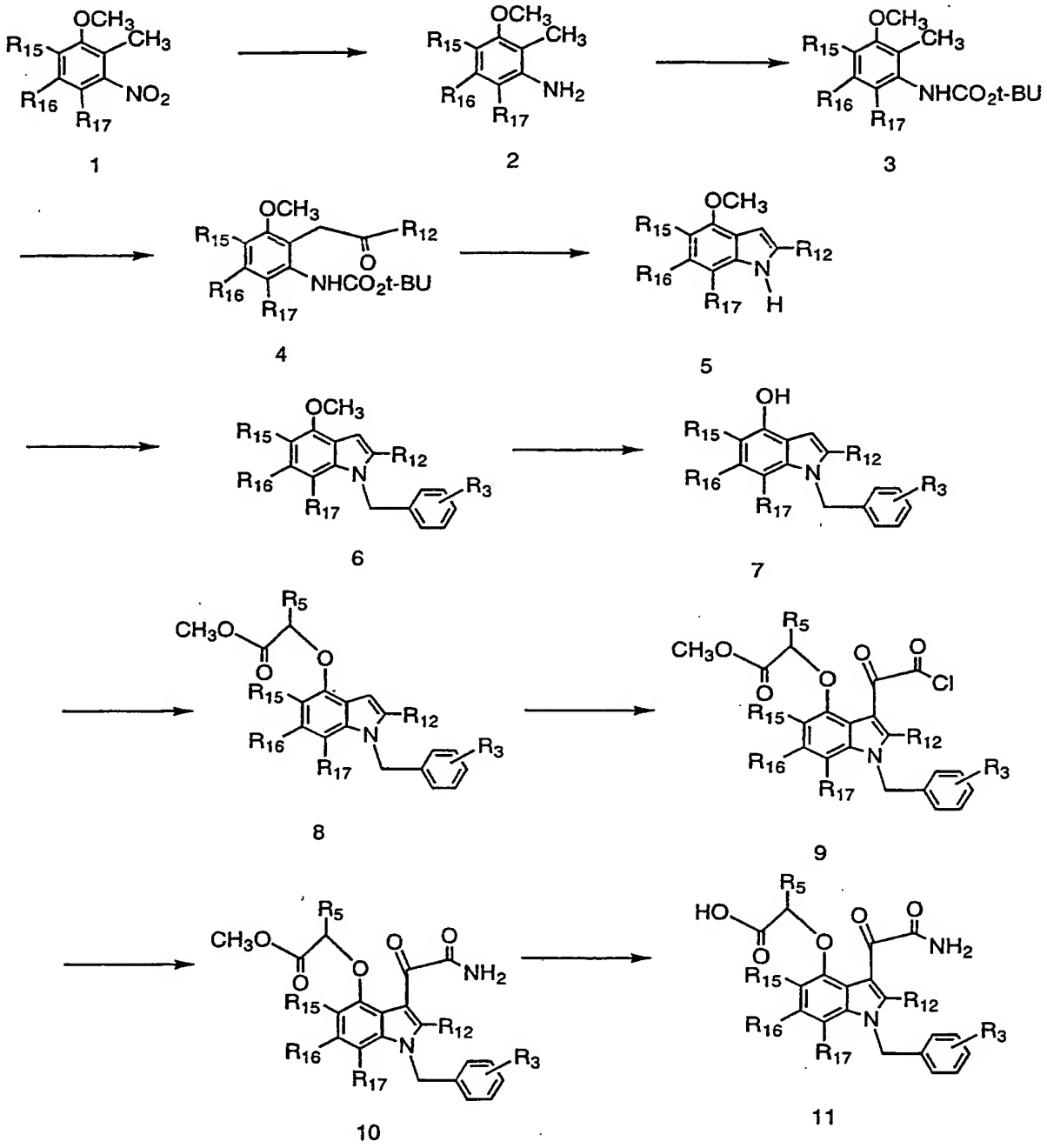
The synthesis of the 1H-indole-3-glyoxylamide compounds may be accomplished as described European Patent Application No. 95302166.4, Publication No. 0 675 110 (publ., 4 October 1995). Further, the synthesis of the indole dicarboxylic acid derivatives may be accomplished as described Japanese Patent Application No. 35984/1997. The synthesis of the indolizine compounds may be accomplished as described WO 9603383 (Publ., 8 February 1996). Such synthetic methods also include well-known methods as recorded in the chemical literature and the procedure illustrated in the following preparative reaction scheme.

The following abbreviations are used throughout the synthesis Schemes and Examples.

Et ethyl

Pr	propyl
t-Bu	t-butyl
Bn	benzyl
LAH	lithium aluminum hydride
THF	tetrahydrofuran
DMF	dimethylformamide
Hex	hexyl

Preparative Reaction Scheme 1



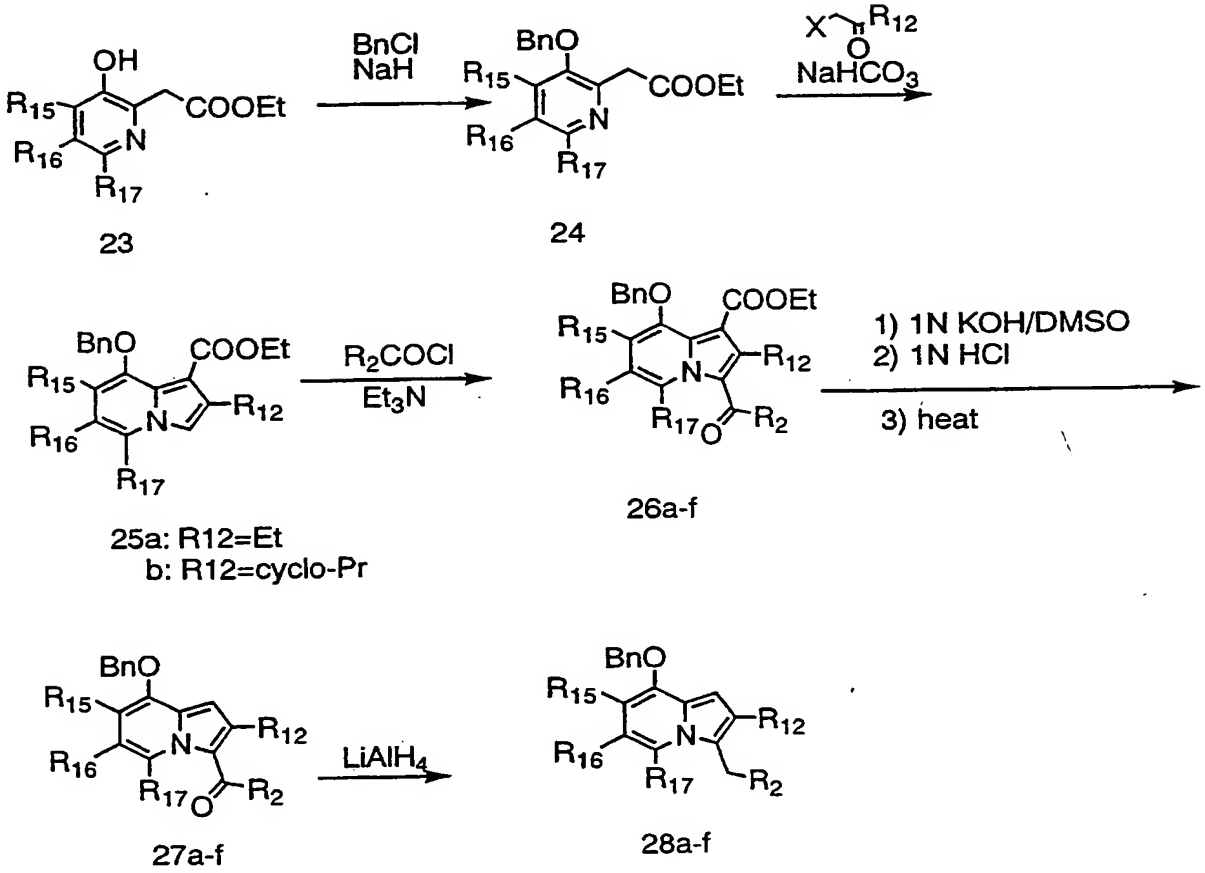
(wherein R12, R15, R16 and R17 are as defined above. R3 is C1-C5 alkyl, aryl, C1-C6 alkoxy, halo, aryloxy, aralkyloxy, nitro, hydroxy, amino, methylamino or dimethylamino. R5 is hydrogen, C1-C10 alkyl, aryl, C1-C10 alkaryl, C1-C10 aralkyl or halo.)

Explanation of Preparative Reaction Scheme 1:

To obtain the glyoxylamides substituted in the 4-position with an acidic function through an oxygen atom, the reactions outlined in scheme 1 are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, Synthesis, 1991, 871-878, the disclosures of which are incorporated herein by reference). The ortho-nitrotoluene, 1, is readily reduced to the 2-methylaniline, 2, using Pd/C as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline, 2, on heating with di-tert-butyl dicarbonate in THF at reflux temperature is converted to the N-tert-butylcarbonyl derivative, 3, in good yield. The dilithium salt of the dianion of 3 is generated at -40 to -20° C in THF using sec-butyl lithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide. This product, 4, may be purified by crystallization from hexane, or reacted directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25° C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated

with an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100° C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, Adv. Drug Res., 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using sodium hydride as a base, with reactions conditions similar to that described for the conversion of 5 to 6. The a-[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10. This product is hydrolyzed using 1N sodium hydroxide in MeOH. The final glyoxylamide, 11, is isolated either as the free carboxylic acid or as its sodium salt or in both forms.

Preparative Reaction Scheme 2 - 1



26-28	R12	R2
a:	Et	Ph
b:	Et	o-Ph-Ph
c:	Et	m-Cl-Ph
d:	Et	m-CF_3-Ph
e:	Et	1-Naphthyl
f:	cyclo-Pr	o-Ph-Ph

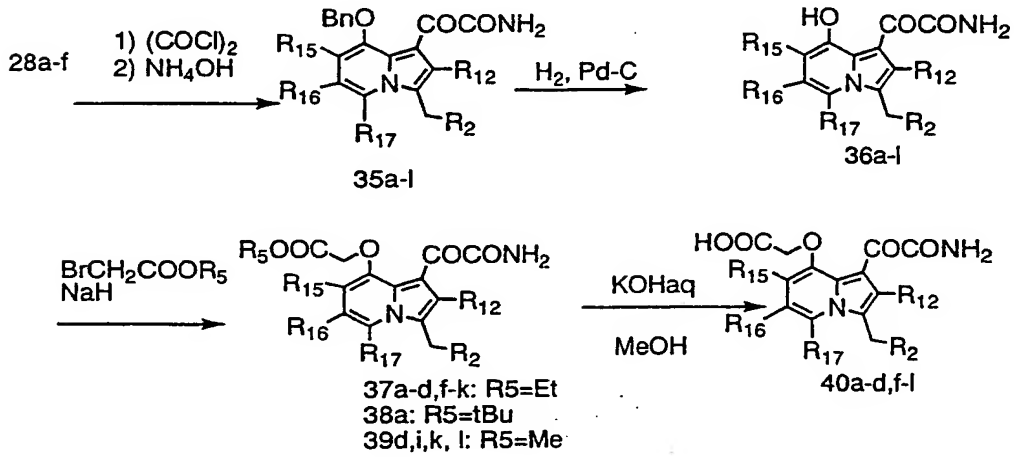
(wherein R12, R15, R16 and R17 are defined above. R2 is C6-C20 alkyl,C6-C20 alkenyl, C6-C20 alkynyl or carbocyclic radical.)

Explanation of Preparative Reaction Scheme 2 - 1:

Compound 23 (N. Desideri F. Mama, M. L. Stein, G. Bile, W. Filippeelli, and E. Marmo, Eur. J. Med. Chem.

Chim. Ther., 18, 295, (1983)) is O-alkylated using sodium hydride and benzyl chloride to give 24. N-alkylation of 24 by 1-bromo-2-butanone or chloromethylcyclopropyl ketone and subsequent base catalyzed cyclization gives 25 which is acylated by aroyl halide to give 26. Hydrolysis of the ester function of 26 followed by acidification forms an acid which is thermally decarboxylated to give 27. Reduction of the ketone function of 27 by LAH yields indolizines 28.

Preparative Reaction Scheme 2 - 2



35-40	R15	R16	R17	R12	R2
a:	H	H	H	Et	Ph
d:	H	H	H	Et	o-Ph-Ph
g:	H	H	H	Me	Ph
h:	H	H	H	Et	m-Cl-Ph
i:	H	H	H	Et	m-CF3-Ph
j:	H	H	H	Et	1-Naphtyl
k:	H	H	H	cyclo-Pr	o-Ph-Ph
l:	H	H	H	Me	cyclo-Hex

(wherein R2, R12, R15, R16 and R17 are as defined above. R5 is hydrogen or C1-C6 alkyl.)

Explanation of Preparative Reaction Scheme 2 - 2:

Sequential treatment of 28 with oxalyl chloride

and ammonium hydroxide forms 35 which is debenzylated by hydrogen in the presence of Pd/C to give 36. Indolizines 36 are O-alkylated using sodium hydride and bromoacetic acid esters to form 37, 38, or 39 which are converted to indolizines 40 by hydrolysis with aqueous base followed by acidification.

Pharmaceutical Formulations

Suitable pharmaceutical formulation of the 1H-indole-3-glyoxylamide compounds may be made as described European Patent Application No. 95302166.4, Publication No. 0 675 110 (publ., 4 October 1995). Suitable pharmaceutical formulation of the indolizine-1-glyoxylamide compounds may be made as described WO 9603383 (publ., 8 February 1996). Formulations may be obtained by conventional procedures well known in the pharmaceutical art.

The 1H-indole-3-glyoxylamide compound or indolizine-1-glyoxylamide compound is generally administered as an appropriate pharmaceutical composition which comprises a therapeutically effective amount of 1H-indole-3-glyoxylamide compound or indolizine-1-glyoxylamide is together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the 1H-indole-3-glyoxylamide compound or indolizine-1-glyoxylamide

compound in the formulation and not deleterious to the subject being treated.

Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc. In tablets the 1H-indole-3-glyoxylamide compound or indolizine-1-glyoxylamide compound is mixed with a carrier having the necessary binding properties in suitable proportions and compacted

in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the 1H-indole-3-glyoxylamide compound or indolizine-1-glyoxylamide compound.

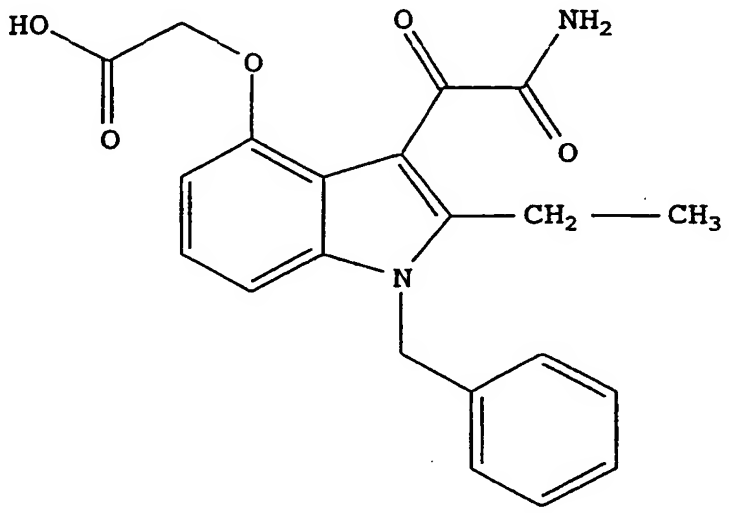
Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both.

EXAMPLES

The following Example 1 illustrates the preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, a 1H-indole-3-glyoxylamide compound useful in the practice of the method of the invention:

Example 1

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, a compound represented by the formula:



Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol) in 250 mL of THF keeping the temperature below -40° C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0° C and then the bath replaced. After the temperature had cooled to -60° C, 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of

ether and 400 mL of 0.5N HCl. The organic layer was separated, washed with water, brine, dried over $MgSO_4$, and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed three times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for $C_{11}H_{13}NO$:

Calculated:	C, 75.40; H, 7.48; N, 7.99
Found:	C, 74.41; H, 7.64; N, 7.97.

Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL(24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.

By the method used in Example 1, Part D, in EP Publication No. 0 675 110, 3.1 g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr_3/CH_2Cl_2 to give a material that was chromatographed on silica gel (eluted with 20 % EtOAc/hexane) to give 1.58 g (54 % yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90 °C.

Analyses for $C_{17}H_{17}NO$:

Calculated:	C, 81.24; H, 6.82; N, 5.57
Found:	C, 81.08; H, 6.92; N, 5.41.

Part D. Preparation of 2-[[2-Ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Using the procedure described in Exmmple 1, Part E, in EP Publication No. 0 675 110, 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56 g, 6.2 mmol) was treated with 248 mg (6.2 mmol) of 60 % NaH/mineral oil and then 0.6 mL (6.2 mmol) of methyl bromoacetate. The product was purified by chromatography over silica gel eluting with 20 % EtOAc/hexane, to give 1.37 g (69 % yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxyl]acetic acid methyl ester, ; mp 89-92 °C.

Analyses for $C_{20}H_{21}NO_3$:

Calculated:	C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Using the procedure in Example F, in EP Publication No. 0 675 110, 1.36 g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester was reacted first with 0.4 mL (4.2 mmol) of oxalyl chloride and then excess ammonia to give a white solid. This was stirred with ethyl acetate and the insoluble material separated and dried to give 1.37 g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187 °C.

Part F. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

A mixture of 788 mg (2mmol) of [3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 10 mL of 1n NaOH and 30 mL of MeOH was heated to maintain reflux for 0.5 hour, stirred at room temperature for 0.5 hour and concentrated at reduced pressure. The residue was taken up in ethyl acetate and water, the aqueous layer separated and made acidic to pH 2-3 with 1N HCl. The precipitate was filtered and washed with ethyl acetate to give 559 mg (74 % yield) of [[3-(2-Amino-1,2-

dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, mp 230-234 °C.

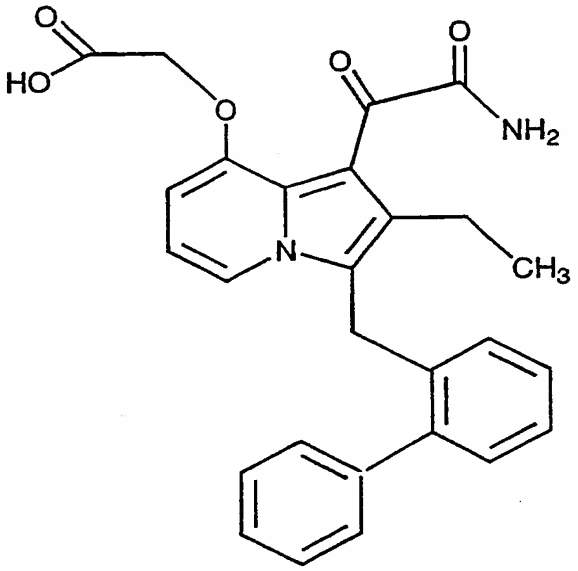
Analyses for $C_{21}H_{20}N_2O_5$:

Calculated:	C, 65.96; H, 5.80; N, 7.33
Found:	C, 66.95; H, 5.55; N, 6.99.

The following Example 2 illustrates the preparation of (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide , a indolizine-1-glyoxylamide compound useful in the practice of the method of the invention:

Example 2

Preparation of (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide, a compound represented by the formula:



Part A: Preparation of Ethyl 3-benzyloxy-2-pyridineacetate 24

60% Sodium hydride (2.69 g, 66.2 m mol) was added in small portions to a solution of ethyl 3-hydroxy-2-pyridineacetate (23, 12.0 g, 66.2 m mol) (N. Desideri, F. Manna, M. L. Stein, G. Bile, W. Filippeelli, and E. Marmo. Eur. J. Med. Chem. Chim. Ther., 18, 295 (1983)) in dimethylformamide (220 ml) at 0 °C. The mixture was stirred at 0 °C for 50 min. Benzyl chloride (8.4 ml, 72.8 m mol) was added dropwise to the mixture, which was stirred overnight. Ethyl acetate was added. The mixture was washed with 5% aqueous sodium hydrogencarbonate and water and dried over Na_2SO_4. After removing the solvent at reduced pressure, the residue

was chromatographed on silica gel eluting with AcOEt:toluene (1:19 to 1:1) to give 16.17 g (90.0% yield) of the titled compound as an oil.

IR ν_{max} (film) 1736, 1446, 1278 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, J=7.2 Hz), 3.93 (2H, s), 4.14 (2H, q, J=7.2 Hz), 5.10 (2H, s), 7.13-7.22 (2H, m), 7.32-7.43 (5H, m), 8.16 (1H, dd, J=4.0, 3.0 Hz). Analyses: Calc'd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.65; H, 6.37; N, 5.20.

Part B: Preparation of Ethyl (8-benzyloxy-2-ethylindolizin-1-yl)carboxylate 25a

A mixture of pyridine derivative (24, 15.15 g, 55.8 m mol) sodium hydrogencarbonate (23.45 g, 279 m mol) and 1-bromo-2-butanone (11.4 ml, 113 m mol) in methylethylketone (250 ml) was heated under reflux for 24 hours, washed with water and dried over Na_2SO_4. After removing the solvent at reduced pressure, the residue was chromatographed on silica gel eluting with AcOEt:hexane (1:19 to 1:9) to give 16.66 g, (92.0% yield) of the titled compound as an oil.

IR ν_{max} (film) 1690, 1227, 1092 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J=7.2 Hz), 1.26 (3H, t, J=7.5 Hz), 2.82 (2H, q, J=7.5 Hz), 4.11 (2H, q, J=7.2 Hz), 5.16 (2H, s), 6.22 (1H, d, J=7.6 Hz), 6.44 (1H, t, J=7.1 Hz), 7.07 (1H, s), 7.27-7.57 (6H, m). Analyses: Calc'd for $C_{20}H_{21}NO_3$ $0.1H_2O$: C, 73.87; H, 6.57; N, 4.31. Found: C, 73.75; H, 6.66; N, 4.30.

Part C: Preparation of Ethyl (8-benzyloxy-2-

ethyl-3-(o-phenylbenzoyl)indolizin-1-yl)carboxylate 26b

A mixture of the indolizine (25, 1 eq), o-phenyl benzoyl chloride (2.0 eq) and triethylamine (5.0 eq) was heated at 90 °C (bath temp.) for 2-8 hours. Ethyl acetate was added. The mixture was washed with dilute hydrochloric acid and water and dried over Na_2SO_4. After removing the solvent at reduced pressure, the residue was chromatographed on silica gel eluting with AcOEt:hexane (1:2) and recrystallized.
Mp, 110-112 ℃ (ether-hexane). 46.0% Yield.

Part D: Preparation of 8-Benzyloxy-2-ethyl-3-(o-phenylbenzoyl)indolizine 27b

To a solution of the ester (26, 1.0 m mol) in dimethylsulfoxide (10 ml), 50% aqueous potassium hydroxide (3 ml) was added. The mixture was heated at 140 °C for 2-24 hours. After cooling, the mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by recrystallization to give the carboxylic acid.
The acid in toluene was heated under reflux for 1 hour and the solvent was removed by distillation at reduced pressure. The residue was purified by recrystallization to give 27.
Quantitative yield. IR ν_{max} (nujol) 1735, 1597, 742 cm^{-1}.

Part E: Preparation of 8-Benzyloxy-2-ethyl-3-(o-phenylbenzyl)indolizine 28b

Compound 27 was treated by the procedure described for the preparation of 4, WO 9603383.
Quantitative yield. IR ν_{max} ($CHCl_3$) 1525, 1259 cm^{-1}.

Part F: Preparation of (8-Benzyloxy-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide 35d

These compounds were prepared according to the procedure described for the synthesis of compound 8 from compound 4, WO 9603383.

Mp, 183-185 °C (ether-hexane). 79.0% Yield.

Part G: Preparation of (2-Ethyl-8-hydroxy-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide 36d

These compounds were prepared according to the procedure described for the synthesis of compound 20 from 19, WO 9603383.

Mp, 195-196 °C (dec.) (ether-hexane). 95.0% Yield.

Part H: Preparation of (8-(Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide 39d

These compounds were prepared according to the procedure described for the synthesis of compound 21 from 20, WO 9603383.

Mp, 73-75 °C (dec.) (ether-hexane). 84% Yield.

Part I: Preparation of (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide

40d

1N-Aqueous potassium hydroxide (4 ml) was added to a solution of the ester (37-39, 2 m mol) in methanol (21 ml). The solution was stirred at room temperature for 40 min, washed with ether, acidified with 2N-HCl and extracted with ethyl acetate. The extracts were washed with water and dried over Na_2SO_4. After removing the solvent at reduced pressure, the residue was recrystallized.

Mp, 209-212 °C (dec.) (ether-hexane). 93% Yield. IR ν_{max} (nujol) 3316, 1704, 1601, 1493 cm^{-1}. ^1H NMR (d_6-DMSO) δ 1.01 (3H, t, J=7.5 Hz), 2.67 (2H, q, J=7.5 Hz), 4.18 (2H, s), 4.71 (2H, s), 6.41 (1H, d, J=7.8 Hz), 6.57-6.59 (2H, m), 7.14-7.57 (10H, m), 7.34 (1H, s), 13.09 (1H, br.s). Analyses: Calc'd for $C_{27}H_{24}N_2O_5$ $0.3H_2O$: C, 70.21; H, 5.37; N, 6.06. Found: C, 70.17; H, 5.35; N, 5.98.

The disorders associated with apoptosis treatment utility of the method of the invention will now be illustrated by the following Example 3 and 4:

Example 3

This example illustrates the action of (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide (the compound prepared in Example 2, hereinafter called "Ex-2") for neuronal death induced by human PLA2-II (hPLA2-II)

(1) Primary culture of neuron

According to a method disclosed in Neurosci. Lett. 203, 175-178 Ueda K. et al, Neuronal cultures were prepared from cerebral cortex of 19-day-old Sprague-Dawley rat embryos. The cerebral cortices were dissociated in isotonic buffer (137mM NaCl, 5.4mM KCl, 0.17mM Na2HPO4, 0.22mM KH2PO4, 5.5mM Glucose, 59mM Sucrose; volume of each buffer is 25 ml) with 4 mg/ml trypsin and 0.4 mg/ml deoxyribonuclease I. Cells were plated at a density of 2.5×10^5 cells/cm^2 on poly-L-lysine coated dishes in conditioning medium, Leibovitz's L-15 medium supplemented with 5 % fetal calf serum and 5 % horse serum. Culture medium was exchanged for conditioning medium containing 0.1 mM arabinosylcytosine C on day 1 after plating. Cultured neurons were used for the experiments on day 2 of culture.

(2) Ultrastructural changes in cortical neurons after PLA_2-II treatment

Cells were treated with $hPLA_2$-II for 48 h, and fixed in situ in 1-5 % (especially 2.5 %) glutaraldehyde in PBS for 2 h at 4 °C and post-fixed in 0.5-2 % (especially 1 %

osmium tetraoxide). To increase contrast, cells were double-fixed in saturated thiocarbohydrazide-osmium. Afterwards, samples were dehydrated using a graded series of ethanol from 50-100 %. Tissue culture dishes were embedded in Araldite or Epoxy resin (especially Epon 812), cured in vacuo for 48 h at 60 -70 °C and sectioned. Afterwards, the culture were double-dyeing with uranium acetate and lead citrate, it was identified the formation by electron microscope. The result was shown in Figure 1. Figure 1A shows the formation of untreated neurons, while Figure 1B shows the formation of hPLA2-II treated neurons.

Result: We confirmed that untreated neurons had bright and round soma, and extended neurites. On the other hand, hPLA2-II-treated neurons had shrank cell bodies and lost their neurites. In comparison with untreated cells (Figure 1A), condensation and fragmentation of nuclear chromatin, lost of intracellular organelle other than mitochondria and blebbing of plasma membranes were observed in hPLA2-II-treated cells (Figure 1B).

(3) Analysis of neuronal survival

For assessment of neurotoxicity of $hPLA_2$-II according to a method disclosed in Neurosci. Lett. 203, 175-178 Ueda K. et al, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide dye (MTT) reduction assay reflecting mitochondrial activity was employed. MTT (5mg/ml) was applied to the conditioning medium (vol/vol = 1/50 - 1/100)

and incubated at 37 ℃ for 1 hour. Supernatant was aspirated and cells were solved by isopropanol containing 0.04 N HCl (100 - 200 ml). Absorbance at 570 nm were measured with a microplate reader.

p-BPB : 100 μ M $hPLA_2$-II were preincubated with 0.01, 0.1 or 1 mM p-bromophenacylbromide for 20 min at 37 °C. After preincubation, an aliquot was removed and diluted 100-fold in the culture medium of cortical neurons.

Vehicle and the compound prepared in Example 2: Cortical neurons were treated with vehicle or 1 μ M $hPLA_2$-II in the presence of the compound prepared in Example 2 at the indicated concentrations on day 2 of culture. MTT reducing activity was determined 48 hr after PLA_2-II-treatment.

The result was shown in Figure 2.

Post-treatment with the compound prepared by Example 2: Cortical neurons were treated with vehicle or 1 μ M hPLA2-II on day 2 of culture. At the indicated time after the treatment with $hPLA_2$-II (1 μ M), the compound prepared in Example 2 (final concentration = 10 μ M) was added to the culture medium. Data are expressed as mean ± SEM values (n = 4). *P < 0.05, **P < 0.01, compared with vehicle-treated conditions by ANOVA followed by Dunnett's test. The result was shown in Figure 3.

Result: From Figure 2, we confirmed that the compound prepared in Example 2 suppressed neuronal death depending on its concentration. From Figure 3, we confirmed that the compound prepared in Example 2

suppressed neuronal death completely within 10 hours after PLA2-II treatment. Thus, posttreatment with a PLA2-II inhibitor, as well as co-treatment, could rescue neuron from PLA2-II-induced death.

Example 4

This example illustrates the action of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid (the compound prepared in Example 1, hereinafter called "Ex-1") for neuronal death induced by human PLA2-II (hPLA2-II)

Analysis of neuronal survival

The experiment was carried out in the same method as in Example 3 (3) mentioned above other than using the 3 μ M instead of 1 μ M in the concentration of hPLA2-II. The result was shown in Figure 4.

Result: From Figure 4, we confirmed that the compound prepared in Example 1 suppressed neuronal death completely depending on its concentration.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30℃ and transferred to a filling device. The required

amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No.45 mesh U.S.sieve and the mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No.14 mesh U.S.sieve. The granules so produced are dried at 50℃ and passed through No.18 mesh U.S.sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No.60 mesh U.S.sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, and magnesium stearate are blended, passed through a No.45 mesh U.S.sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2000 mg
Total	2225 mg

The active ingredient is passed through a No.60 mesh U.S.sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg

Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No.45 mesh U.S.sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

Brief Description of Drawings

Figure 1A shows the formation of untreated neurons.

Figure 1B shows the formation of hPLA2-II-treated neurons.

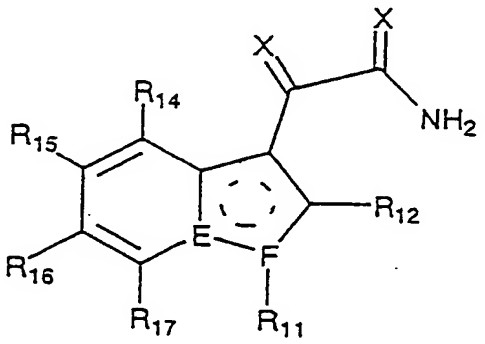
Figure 2 shows the action of Ex-2 for neuronal death induced by hPLA2-II. (Concentration-course)

Figure 3 shows the action of Ex-2 for neuronal death induced by hPLA2-II. (Time-course)

Figure 4 shows the action of Ex-1 for neuronal death induced by hPLA2-II. (Concentration-course)

Claims

1. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal a therapeutically effective amount of an N-heterocyclic glyoxylamide compound represented by the formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(I)

wherein ;

E and F are differently C or N;

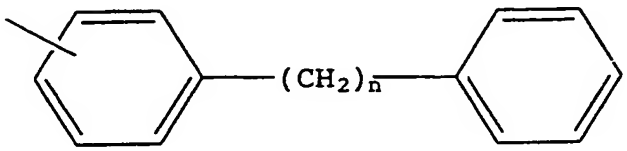
---- is presence or absence of a double bond;

each X is independently oxygen or sulfur;

R_{11} is selected from groups (a), (b) and (c) where;

(a) is C_7-C_{20} alkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl; or carbocyclic radical selected from the group cycloalkyl, cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,

biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),

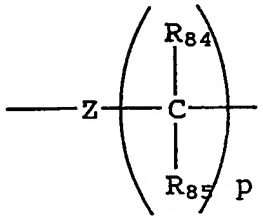


(bb)

where n is a number from 1 to 8; or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8;

(c) is the group -(L_1)-R_{81}; where, -(L_1)- is a divalent linking group having the formula;



where,

R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, carbolxy, carbalkoxy, or halo;

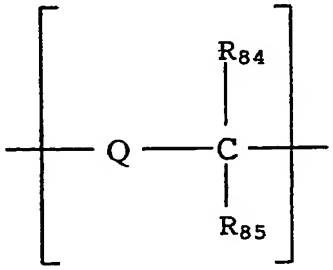
p is 1 to 5,

Z is a bond, -(CH_2)-, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

where R_{81} is a group selected from (a) or (b);

R_{12} is hydrogen, halo, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_3-C_4 cycloalkenyl, -O-(C_1-C_2 alkyl), or -S-(C_1-C_2 alkyl);

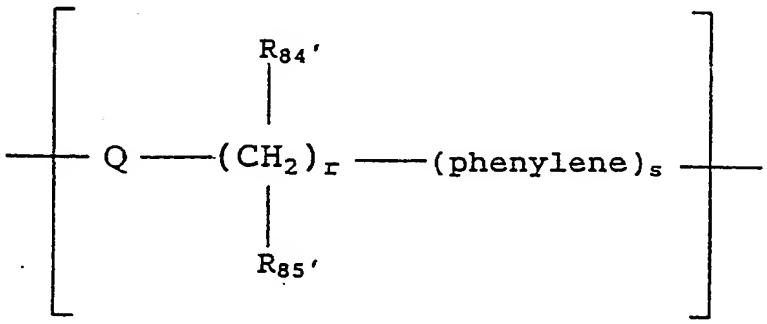
R_{14} is hydrogen or a group, -(L_a)-(acidic group) wherein -(L_a)- is represented by the formula;



where Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84} and R_{85} are each independently

selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, and halo;

R_{15} is hydrogen or a group, -(L_a')-(acidic group) wherein -(L_a')- is represented by the formula;



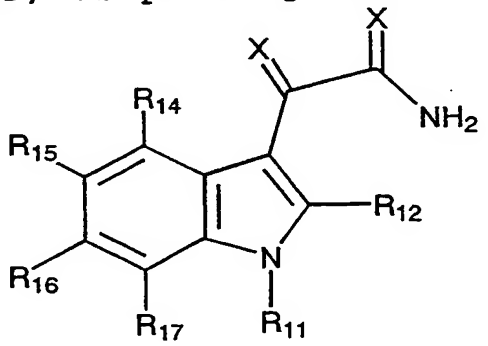
where r is a number from 1 to 7, s is 0 or 1, and Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84}' and R_{85}' are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, carboxy, carbalkoxy, and halo; provided that at least one of R14 or R15 must be the group, -(La)-(acidic group) or -(La')-(acidic group);

R_{16} is hydrogen, carboxyl or ester thereof;

R_{17} is selected from hydrogen, non-interfering substituents, selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12}

alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_2-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8.

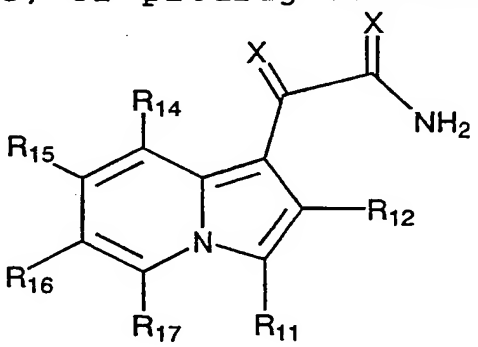
2. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal a therapeutically effective amount of a 1H-indole-3-glyoxylamide compound represented by the formula (II) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(II)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

3. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal a therapeutically effective amount of an indolizine-1-glyoxylamide compound represented by the formula (III) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(III)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

4. The method of claim 2 or 3 wherein for the compound of formula (II) or (III) both X are oxygen, only one of R14 or R15 are -(La)-(acidic group) or -(La')-(acidic group) and the (acidic group) is carboxyl.

5. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate,

or a prodrug derivative thereof selected from the group consisting of compounds (A) through (NN):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(B) dl-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]propanoic acid,

(C) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(E) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-4-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(F) [[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(G) [[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(L) [[3-(2-amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-propyl-1H-indol-4-yl]oxy]acetic acid,

(M) [[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(N) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-cyclopropyl-1H-indol-4-yl]oxy]acetic acid,

(O) 4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,

(P) mixtures of (A) through (O),

(Q) (8-(Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(R) (3-Benzyl-8-(carbethoxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(S) (8-(Carbethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(T) (3-Benzyl-8-(carbethoxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(U) (8-(Carbethoxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(V) (8-Carbethoxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(W) (3-Benzyl-8-(t-

butoxycarbonylmethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(X) (8-(Carbmethoxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(Y) (8-(Carbmethoxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(Z) (3-Benzyl-8-(carboxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(BB) (3-Benzyl-8-(carboxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(CC) (8-(Carboxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(DD) (8-(Carboxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(EE) (8-Carboxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(FF) (8-(Carboxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(GG) mixtures of (Q) through (FF),

(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(JJ) [[3-(2-Amino-1,2-dioxoethyl)-6-ethoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(KK) [[3-(2-Amino-1,2-dioxoethyl)-6-n-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(LL) [[3-(2-Amino-1,2-dioxoethyl)-6-i-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(MM) [[3-(2-Amino-1,2-dioxoethyl)-6-cyclopropyloxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(NN) mixtures of (HH) through (MM).

6. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof selected from the group consisting of compounds (I) and (I'):

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

7. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof selected from the group consisting of compounds (A), (D), (H), (J) and (K):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid.

8. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate,

or a prodrug derivative thereof selected from the group consisting of compounds (AA) and (AA'):

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

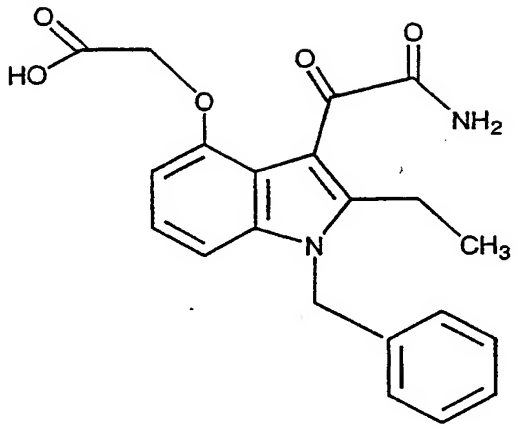
(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide.

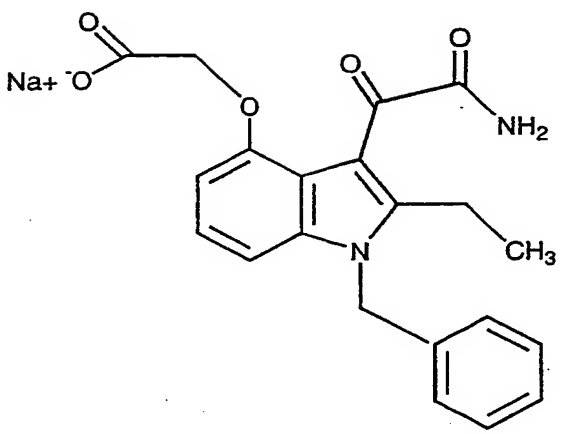
9. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof selected from the group consisting of compounds (HH) and (II):

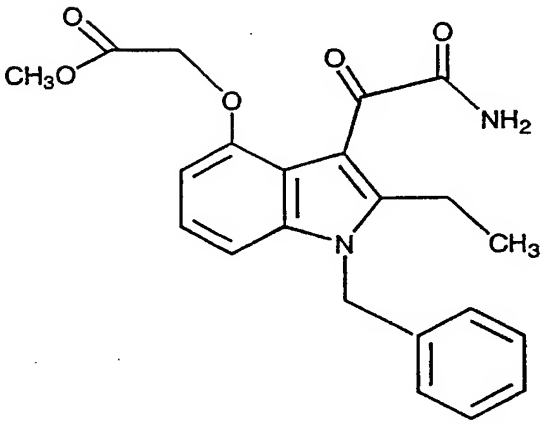
(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

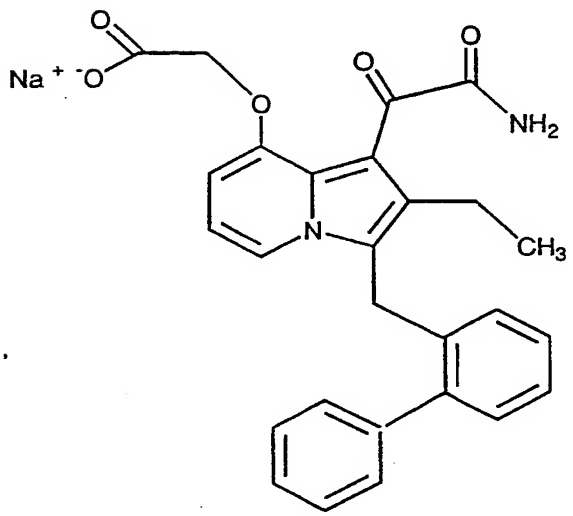
(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid.

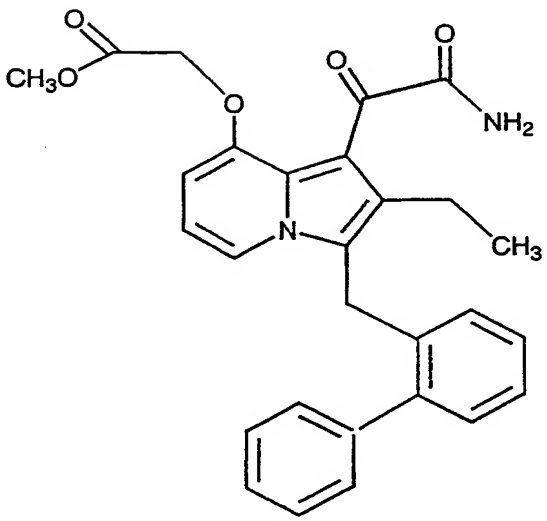
10. A method of treatment of a mammal currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of an N-heterocyclic glyoxylamide compound selected from the formula:

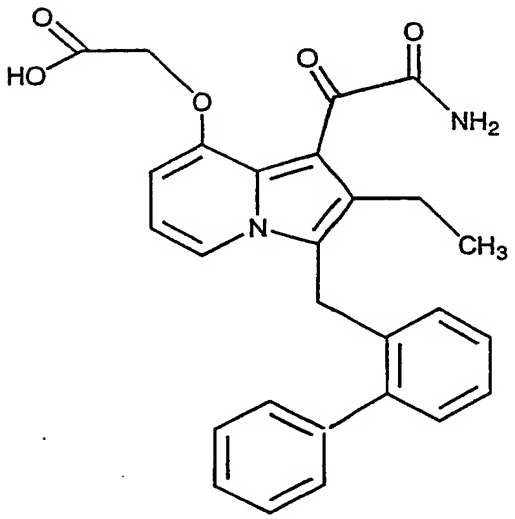


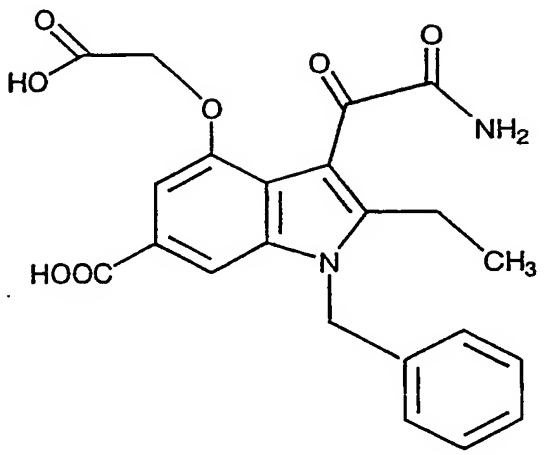


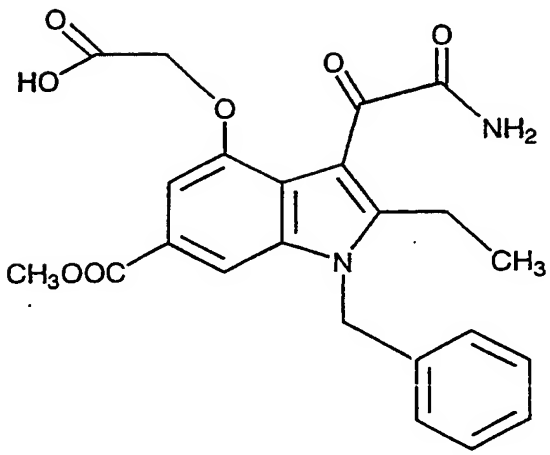




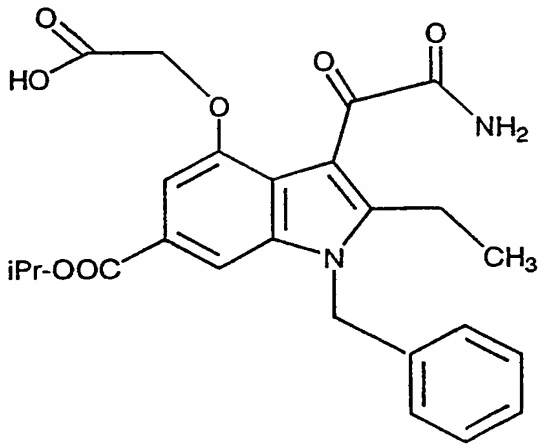








or



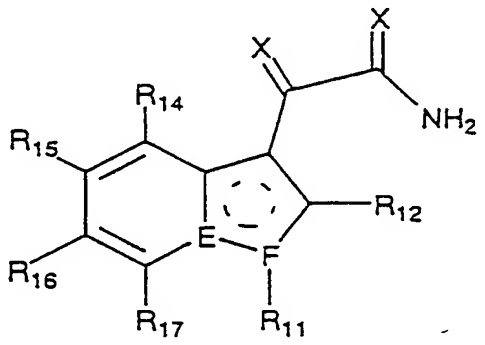
or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof.

11. The method of claims 1 or 2 or 3 or 4 or 5 or 6 wherein the therapeutically effective amount of the compound is in the form of a pharmaceutical formulation comprising the compound and a suitable carrier or excipient therefor.

12. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated

with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is represented by the formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(I)

wherein ;

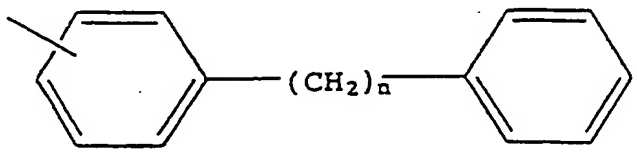
E and F are differently C or N;

---- is presence or absence of a double bond;

each X is independently oxygen or sulfur;

R_{11} is selected from groups (a), (b) and (c) where;

(a) is C_7-C_{20} alkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl; or carbocyclic radical selected from the group cycloalkyl, cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),

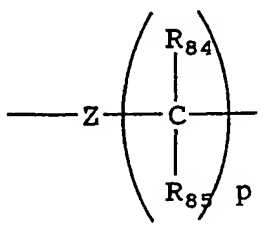


(bb)

where n is a number from 1 to 8; or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8;

(c) is the group -(L_1)-R_{81}; where, -(L_1)- is a divalent linking group having the formula;



where,

R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, carbolxy, carbalkoxy, or halo;

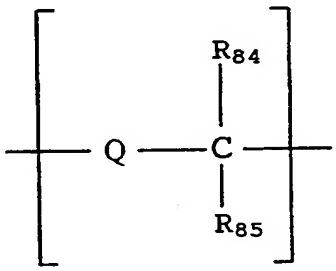
p is 1 to 5,

Z is a bond, $-(CH_2)-$, -O-, $-N(C_1-C_{10}$ alkyl)-, -NH-, or -S-; and

where R_{81} is a group selected from (a) or (b);

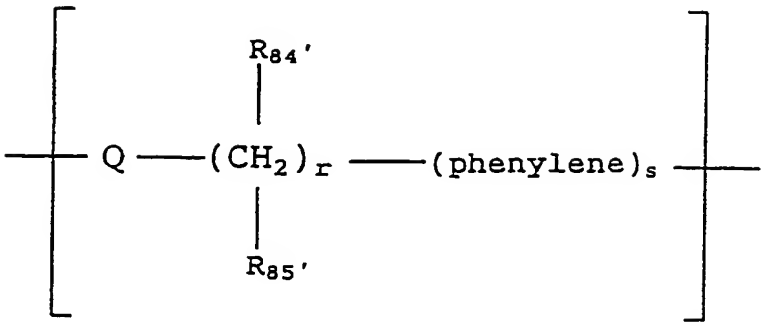
R_{12} is hydrogen, halo, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_3-C_4 cycloalkenyl, $-O-(C_1-C_2$ alkyl), or $-S-(C_1-C_2$ alkyl);

R_{14} is hydrogen or a group, $-(L_a)-$(acidic group) wherein $-(L_a)-$ is represented by the formula;



where Q is selected from the group $-(CH_2)-$, -O-, -NH-, and -S-, and R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, and halo;

R_{15} is hydrogen or a group, $-(L_a')-$(acidic group) wherein $-(L_a')-$ is represented by the formula;



where r is a number from 1 to 7, s is 0 or 1, and Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84}' and R_{85}' are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, carboxy, carbalkoxy, and halo; provided that at least one of R14 or R15 must be the group, -(La)-(acidic group) or -(La')-(acidic group);

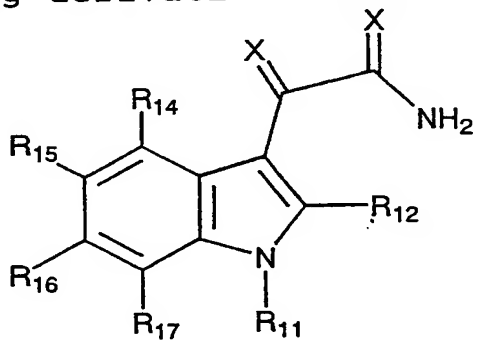
R_{16} is hydrogen, carboxyl or ester thereof;

R_{17} is selected from hydrogen, non-interfering substituents, selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_2-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -(CH_2)$_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO,

amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8.

13. Use of a 1H-indole-3-glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is represented by the formula (II) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



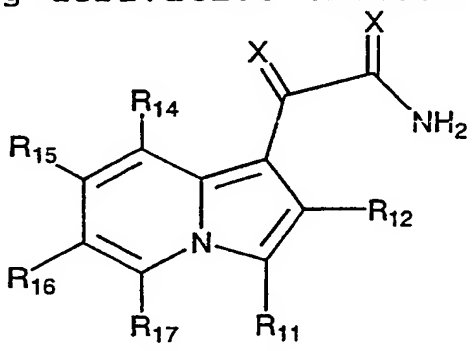
(II)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

14. Use of an indolizine-1-glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted

with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is represented by the formula (III) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(III)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

15. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (A) through (NN):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(B) dl-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]propanoic acid,

(C) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(E) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-4-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(F) [[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(G) [[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(L) [[3-(2-amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-propyl-1H-indol-4-yl]oxy]acetic acid,

(M) [[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(N) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-cyclopropyl-1H-indol-4-yl]oxy]acetic acid,

(O) 4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,

(P) mixtures of (A) through (O),

(Q) (8-(Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(R) (3-Benzyl-8-(carbethoxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(S) (8-(Carbethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(T) (3-Benzyl-8-(carbethoxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(U) (8-(Carbethoxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(V) (8-Carbethoxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(W) (3-Benzyl-8-(t-butoxycarbonylmethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(X) (8-(Carbmethoxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(Y) (8-(Carbmethoxymethyloxy)-2-

cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(Z) (3-Benzyl-8-(carboxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(BB) (3-Benzyl-8-(carboxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(CC) (8-(Carboxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(DD) (8-(Carboxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(EE) (8-Carboxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(FF) (8-(Carboxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(GG) mixtures of (Q) through (FF),

(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(JJ) [[3-(2-Amino-1,2-dioxoethyl)-6-ethoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(KK) [[3-(2-Amino-1,2-dioxoethyl)-6-n-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(LL) [[3-(2-Amino-1,2-dioxoethyl)-6-i-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(MM) [[3-(2-Amino-1,2-dioxoethyl)-6-cyclopropyloxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(NN) mixtures of (HH) through (MM).

16. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (I) and (I'):

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

17. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (A), (D), (H), (J) and (K):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid.

18. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

where the compound is an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (AA) and (AA'):

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-

phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide.

19. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

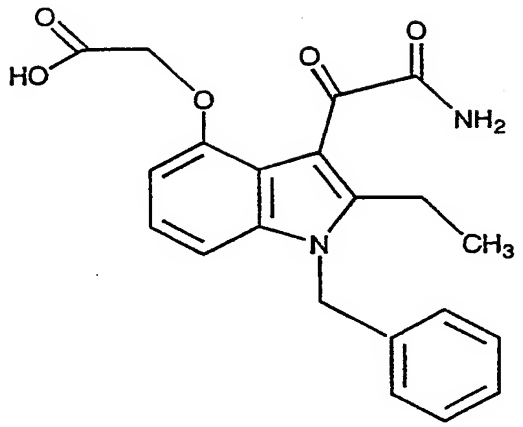
where the compound is an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (HH) and (II):

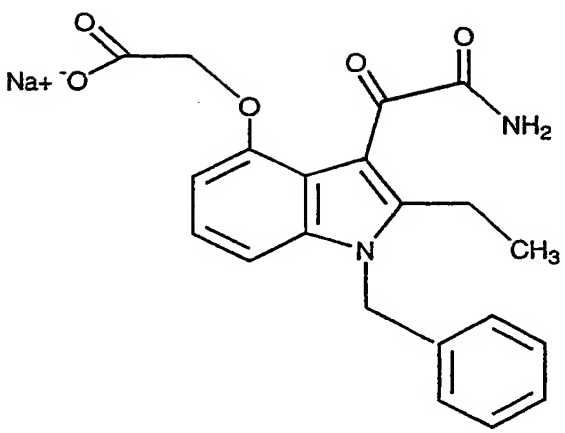
(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

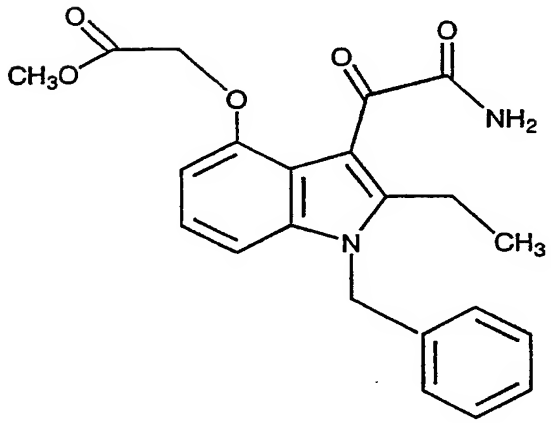
(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid.

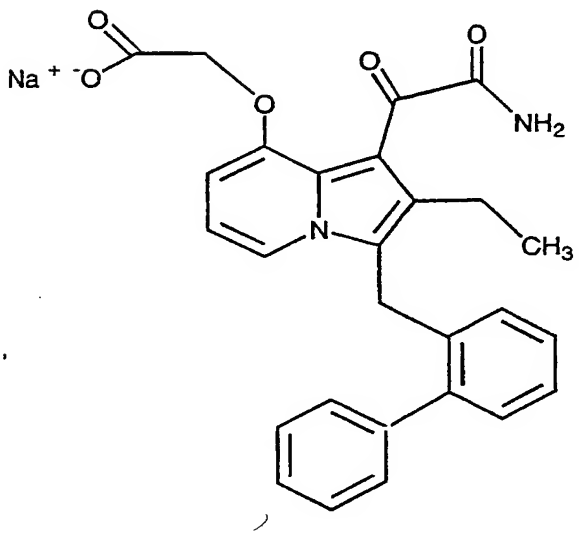
20. Use of an N-heterocyclic glyoxylamide compound for the manufacture of a medicant for treating disorders associated with apoptosis in a mammal, including a human, currently afflicted with disorders associated with apoptosis or previously afflicted with disorders associated with apoptosis;

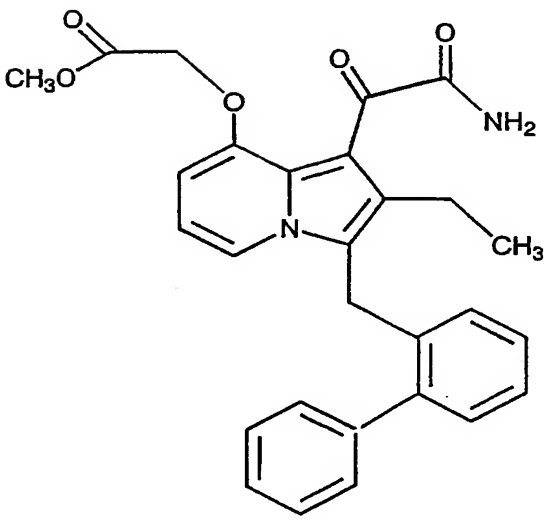
where the compound is an N-heterocyclic glyoxylamide compound selected from the formula:

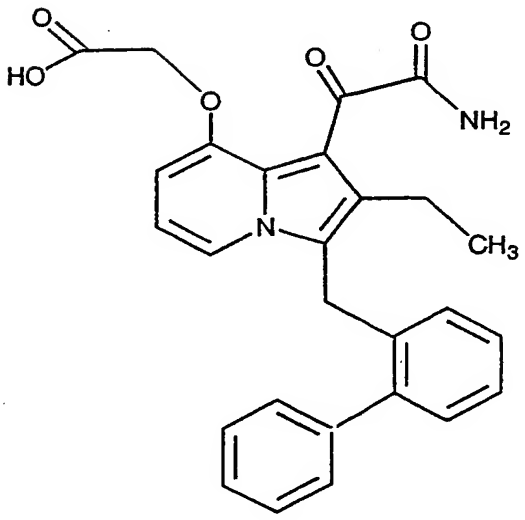


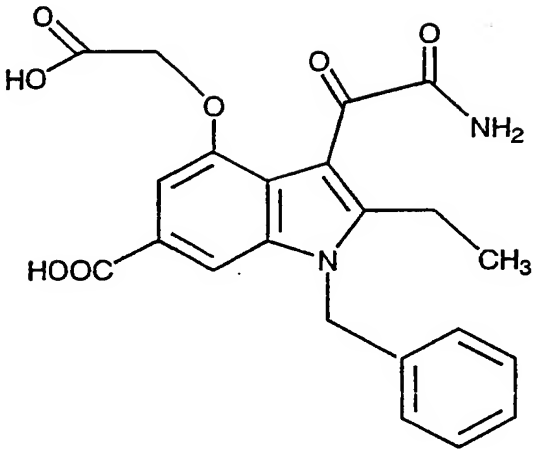


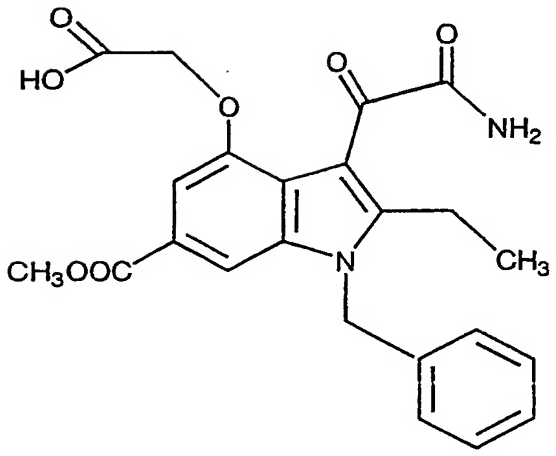




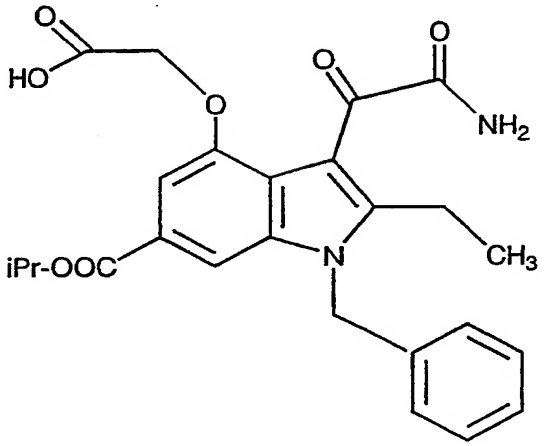








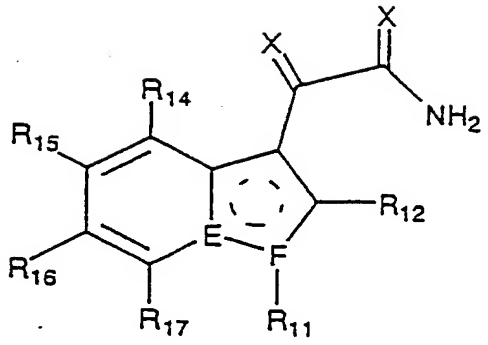
or



or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof.

21. A composition for treatment of disorders associated with apoptosis;

which comprises an N-heterocyclic glyoxylamide compound represented by the formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(I)

wherein ;

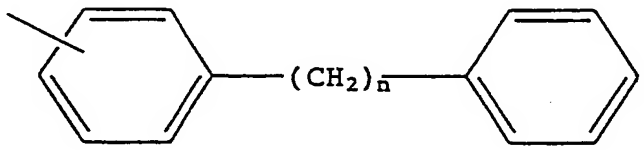
E and F are differently C or N;

----- is presence or absence of a double bond;

each X is independently oxygen or sulfur;

R_{11} is selected from groups (a), (b) and (c) where;

(a) is C_7-C_{20} alkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl; or carbocyclic radical selected from the group cycloalkyl, cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),



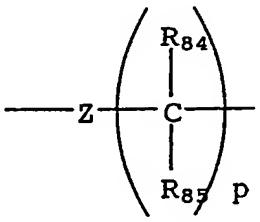
(bb)

where n is a number from 1 to 8; or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents selected from the group consisting of

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8;

(c) is the group -(L_1)-R_{81}; where, -(L_1)- is a divalent linking group having the formula;



where,

R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, carbolxy, carbalkoxy, or halo;

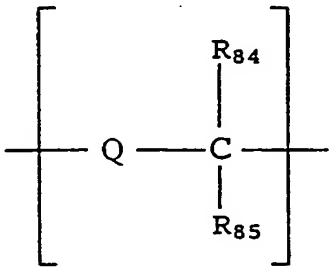
p is 1 to 5,

Z is a bond, $-(CH_2)-$, $-O-$, $-N(C_1-C_{10}$ alkyl$)-$, $-NH-$, or $-S-$; and

where R_{81} is a group selected from (a) or (b);

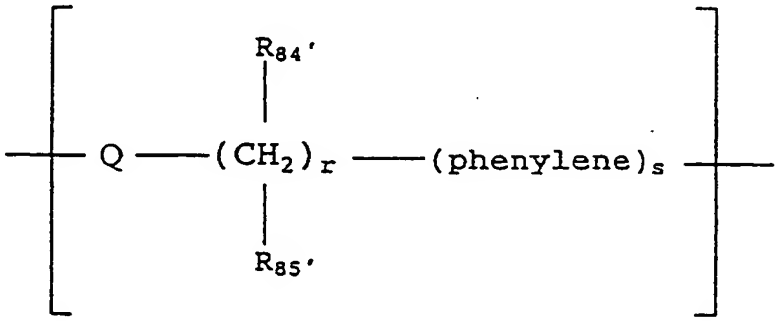
R_{12} is hydrogen, halo, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_3-C_4 cycloalkenyl, $-O-(C_1-C_2$ alkyl$)$, or $-S-(C_1-C_2$ alkyl$)$;

R_{14} is hydrogen or a group, $-(L_a)-$(acidic group) wherein $-(L_a)-$ is represented by the formula;



where Q is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, and $-S-$, and R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, and halo;

R_{15} is hydrogen or a group, $-(L_a')-$(acidic group) wherein $-(L_a')-$ is represented by the formula;



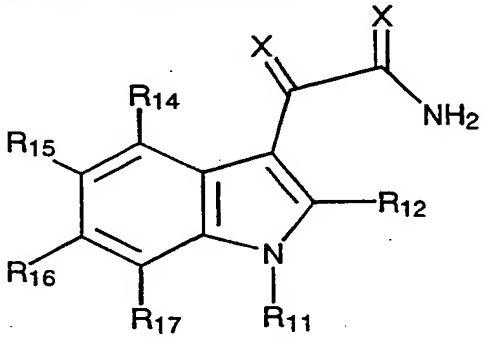
where r is a number from 1 to 7, s is 0 or 1, and Q is selected from the group -(CH_2)-, -O-, -NH-, and -S-, and R_{84}' and R_{85}' are each independently selected from hydrogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} alkaryl, C_1-C_{10} aralkyl, carboxy, carbalkoxy, and halo; provided that at least one of R14 or R15 must be the group, -(La)-(acidic group) or -(La')-(acidic group);

R_{16} is hydrogen, carboxyl or ester thereof;

R_{17} is selected from hydrogen, non-interfering substituents, selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_2-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -(CH_2)n-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH_2)$_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and C_1-C_6 carbonyl; where n is from 1 to 8.

22. A composition for treatment of disorders associated with apoptosis;

which comprises a 1H-indole-3-glyoxylamide compound represented by the formula (II) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:

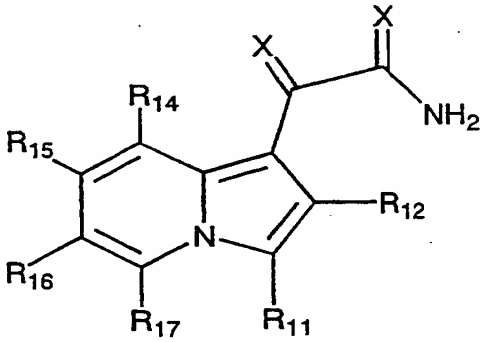


(II)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

23. A composition for treatment of disorders associated with apoptosis;

which comprises an indolizine-1-glyoxylamide compound represented by the formula (III) or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof:



(III)

wherein X, R_{11}, R_{12}, R_{14}, R_{15}, R_{16} and R_{17} are as defined above.

24. A composition for treatment of disorders associated with apoptosis;

which comprises an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (A) through (NN):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(B) dl-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]propanoic acid,

(C) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(E) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-4-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(F) [[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(G) [[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(L) [[3-(2-amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-propyl-1H-indol-4-yl]oxy]acetic acid,

(M) [[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(N) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-cyclopropyl-1H-indol-4-yl]oxy]acetic acid,

(O) 4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,

(P) mixtures of (A) through (O),

(Q) (8-(Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(R) (3-Benzyl-8-(carbethoxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(S) (8-(Carbethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(T) (3-Benzyl-8-(carbethoxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(U) (8-(Carbethoxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(V) (8-Carbethoxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(W) (3-Benzyl-8-(t-butoxycarbonylmethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(X) (8-(Carbmethoxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(Y) (8-(Carbmethoxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(Z) (3-Benzyl-8-(carboxymethyloxy)-2-ethylindolizin-1-yl)glyoxylamide,

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(BB) (3-Benzyl-8-(carboxymethyloxy)-2-methylindolizin-1-yl)glyoxylamide,

(CC) (8-(Carboxymethyloxy)-3-(m-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide,

(DD) (8-(Carboxymethyloxy)-2-ethyl-3-(m-trifluoromethylbenzyl)indolizin-1-yl)glyoxylamide,

(EE) (8-Carboxymethyloxy-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide,

(FF) (8-(Carboxymethyloxy)-2-cyclopropyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(GG) mixtures of (Q) through (FF),

(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(JJ) [[3-(2-Amino-1,2-dioxoethyl)-6-ethoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(KK) [[3-(2-Amino-1,2-dioxoethyl)-6-n-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(LL) [[3-(2-Amino-1,2-dioxoethyl)-6-i-propoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(MM) [[3-(2-Amino-1,2-dioxoethyl)-6-cyclopropyloxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

(NN) mixtures of (HH) through (MM).

25. A composition for treatment of disorders associated with apoptosis;

which comprises an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (I) and (I'):

(I) [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(I') [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

26. A composition for treatment of disorders associated with apoptosis;

which comprises an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (A), (D), (H), (J) and (K):

(A) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,

(D) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-3-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid,

(H) [[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthalenyl)methyl]-1H-indol-4-yl]oxy]acetic acid,

(J) [[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,

(K) [[3-(2-Amino-1,2-dioxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-ethyl-1H-indol-4-yl]oxy]acetic acid.

27. A composition for treatment of disorders associated with apoptosis;

which comprises an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (AA) and (AA'):

(AA) (8-(Carboxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide,

(AA') (8-Carbomethoxymethyloxy)-2-ethyl-3-(o-phenylbenzyl)indolizin-1-yl)glyoxylamide.

28. A composition for treatment of disorders associated with apoptosis;

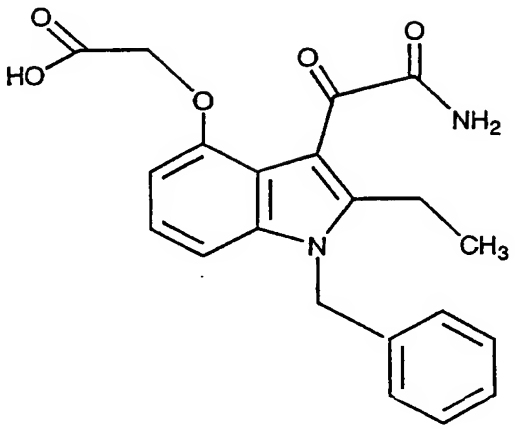
which comprises an N-heterocyclic glyoxylamide compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof selected from the group consisting of compounds (HH) and (II):

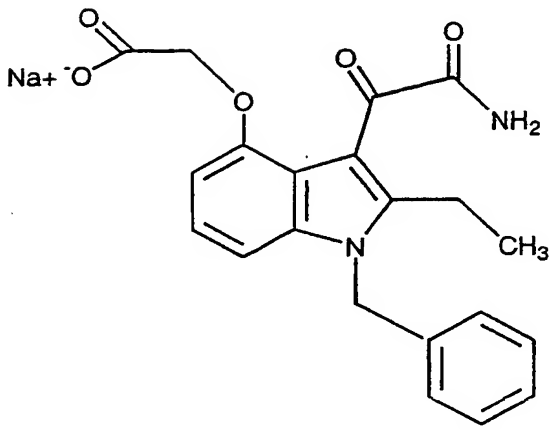
(HH) [[3-(2-Amino-1,2-dioxoethyl)-6-carboxyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid,

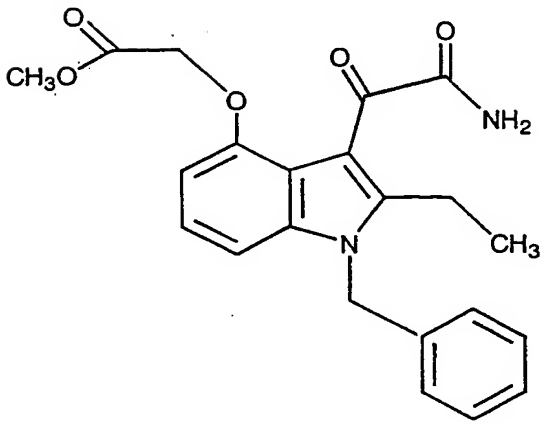
(II) [[3-(2-Amino-1,2-dioxoethyl)-6-methoxycarbonyl-2-ethyl-1-benzyl-1H-indol-4-yl]oxy]acetic acid.

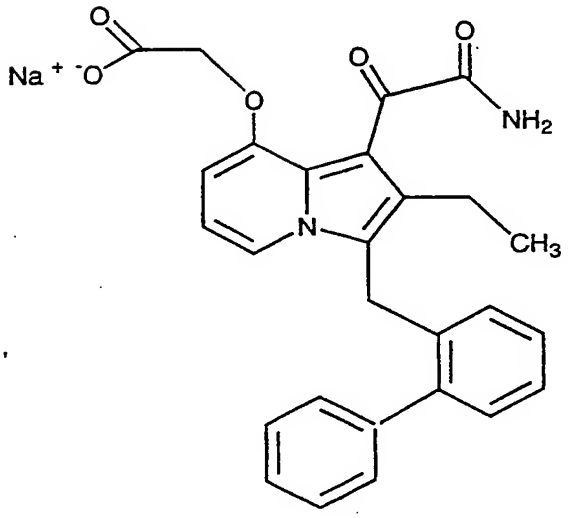
29. A composition for treatment of disorders associated with apoptosis;

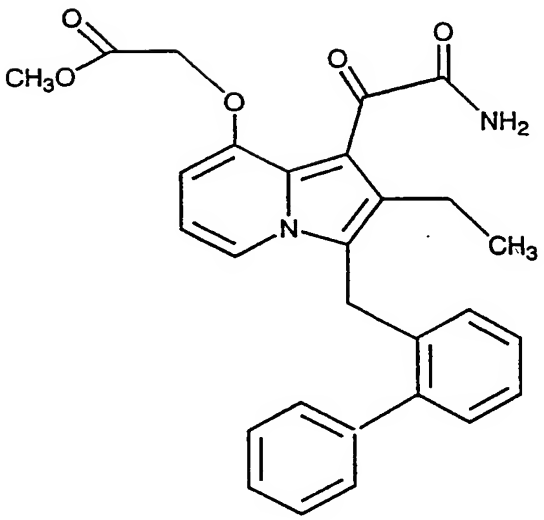
which comprises an N-heterocyclic glyoxylamide compound selected from the formula:

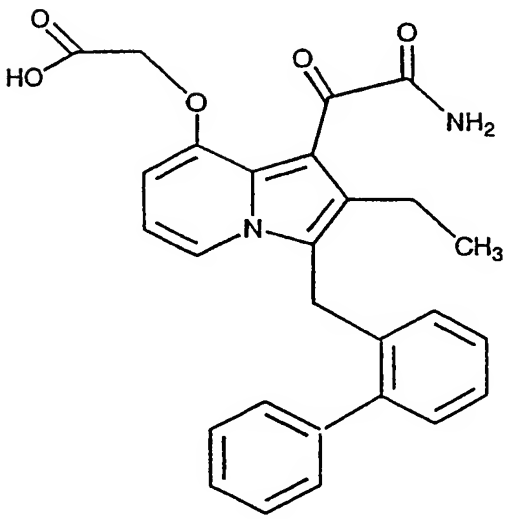


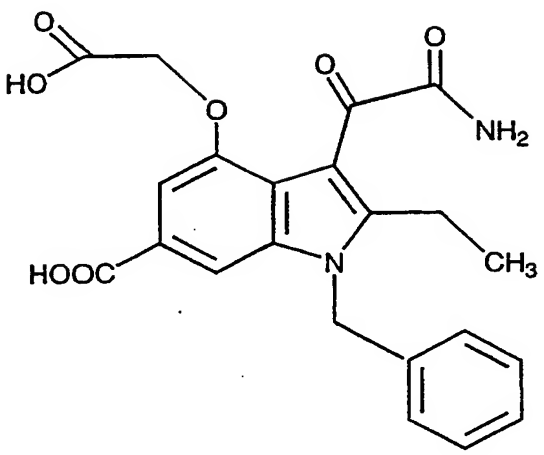


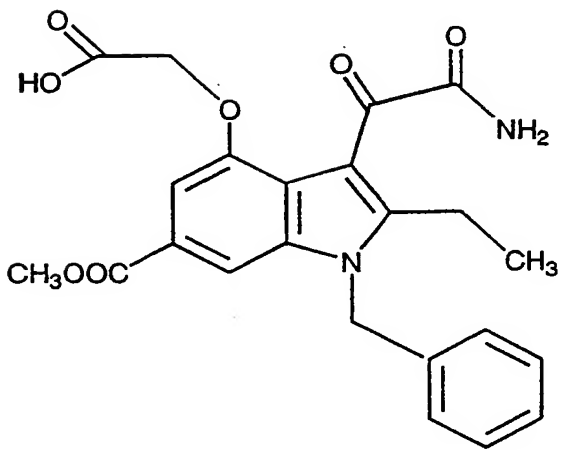




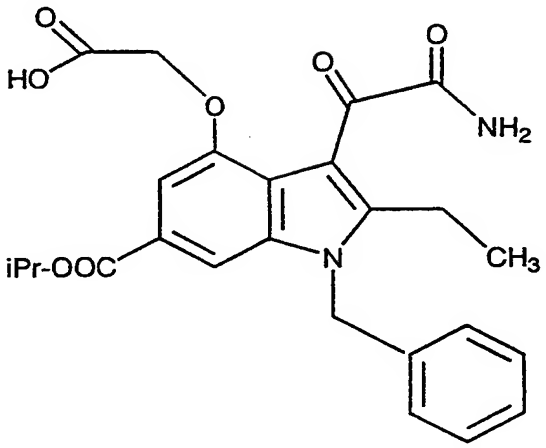








or



or a pharmaceutically acceptable salt, solvate, or a prodrug derivative thereof.

Fig. 1

(A) control

Fig. 1

(B) hPLA2-II

Fig. 2

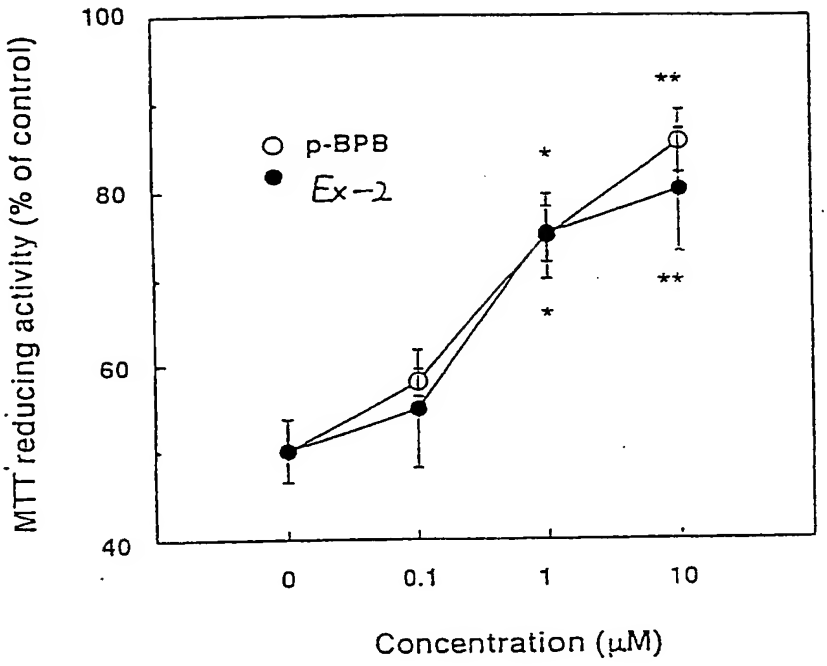

MTT reducing activity (% of control)
100
80
60
40
0
0.1
1
10
Concentration (μM)
p-BPB
Ex-2
**
*
*
**

Fig. 3

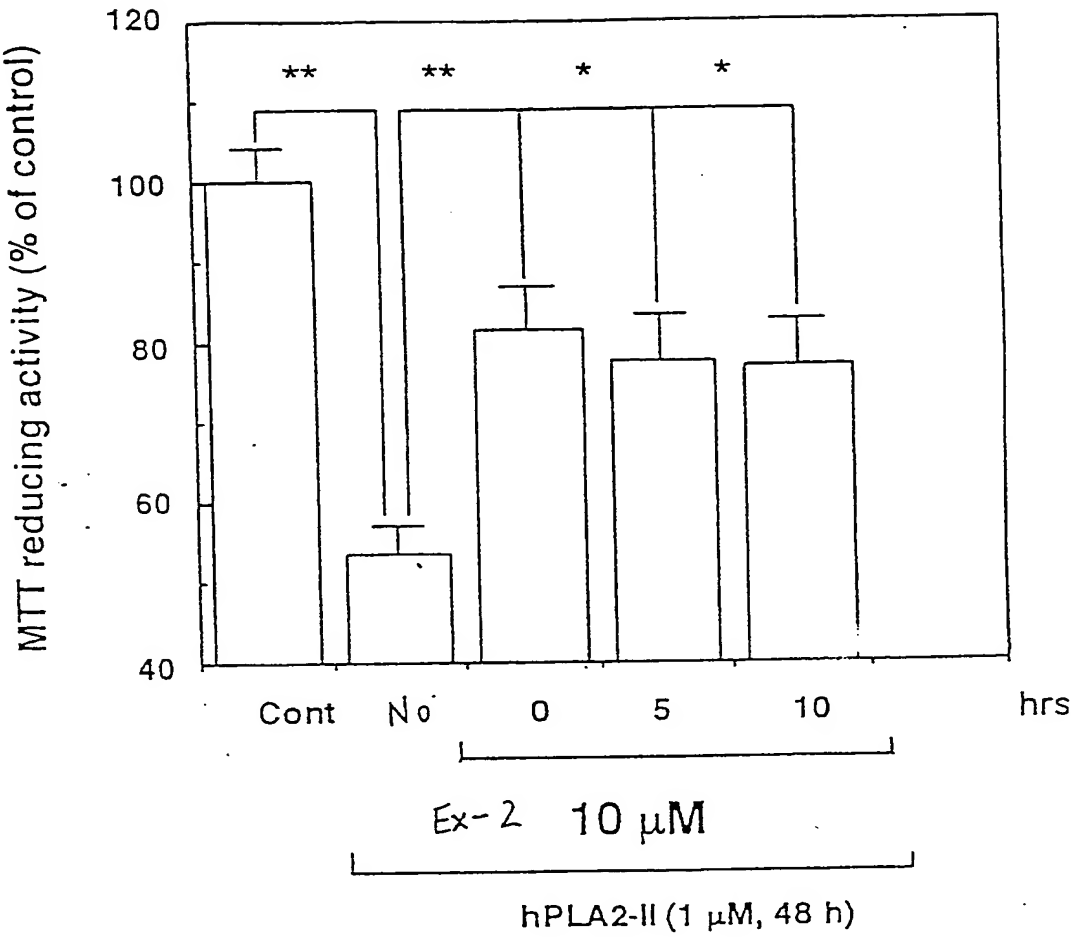
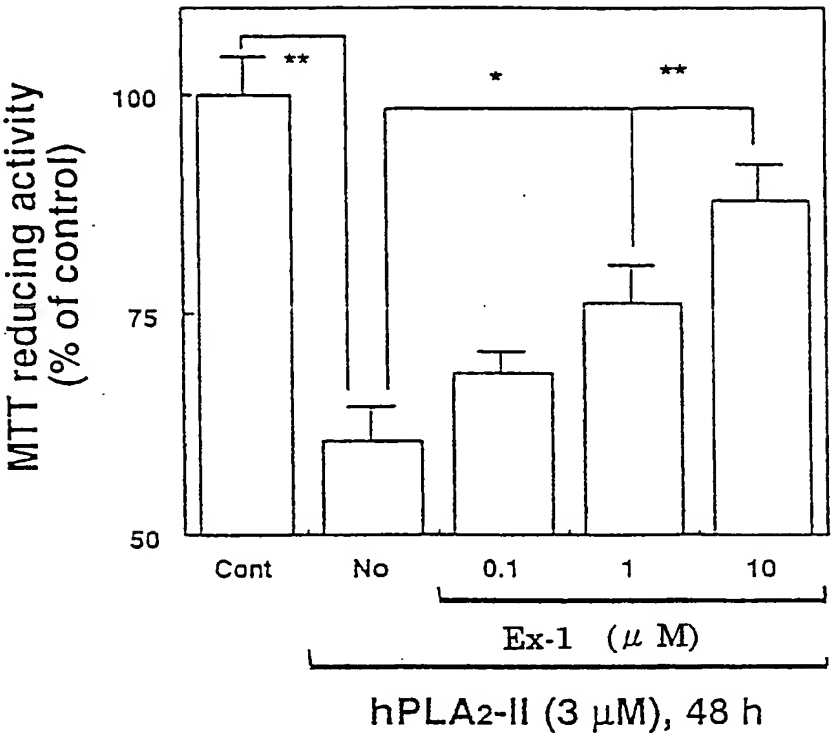

120
100
80
60
40
MTT reducing activity (% of control)
**
**
*
*
Cont
No
0
5
10
hrs
Ex-2 10 μM
hPLA2-II (1 μM, 48 h)

Fig. 4



INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/JP 97/04104

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 675 110 A (LILLY CO ELI) 4 October 1995 cited in the application see page 32, line 34 - page 33, line 45; claims 1-10; examples 1-17 ---	1,2,4-7, 9-13, 15-17, 19-22, 24-26, 28,29
X	WO 96 03383 A (LILLY CO ELI ;SHIONOGI & CO (JP); DILLARD ROBERT D (US); HAGISHITA) 8 February 1996 cited in the application see page 160, line 30 - page 161, line 24; claims 1-32 --- -/--	1,3-5,8, 10-12, 14,15, 18,20, 21,23, 24,27,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1998	21.08.98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer A. Jakobs

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/JP 97/04104

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DRAHEIM ET AL.: "Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A2. 3. Indole-3-glyoxamides" J. MED. CHEM., vol. 39, no. 26, 1996, pages 5159-5175, XP002073103 see table 1 ---	1,2,4-7, 9-13, 15-17, 19-22, 24-26, 28,29
A	WO 96 40982 A (ATHENA NEUROSCIENCES INC ;RYDEL RUSSEL E (US); DAPPEN MICHAEL S (U) 19 December 1996 see page 9, line 4-23 see page 28, line 15 - page 29, line 15 ---	1-29
A	WO 95 17183 A (LILLY CO ELI) 29 June 1995 see page 2, line 11 - page 4, line 14 ---	1-29
A	GONZALO J A ET AL: "LINOMIDE, A NOVEL IMMUNOMODULATOR THAT PREVENTS DEATH IN FOUR MODELS OF SEPTIC SHOCK" EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 23, no. 9, 1 January 1993, pages 2372-2374, XP000568243 see concluding remarks see page 2372, column 1, line 1 - column 2, line 20 -----	1-29

1

INTERNATIONAL SEARCH REPORT

Ir. ıational application No.
PCT/JP 97/04104

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-11 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

in view of the large number of compounds, which are defined by the general definition in the indipendent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application. (See Guidelines, Chapter III, paragraph 2.3).
Figure 1 on page 55 and figure 1 on page 69 contain hexvalent carbon atoms.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ..tal Application No
PCT/JP 97/04104

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0675110 A	04-10-1995	AU 688458 B	12-03-1998
		AU 1621795 A	12-10-1995
		BR 9501404 A	05-03-1996
		CA 2146097 A	02-10-1995
		CN 1114310 A	03-01-1996
		CZ 9500822 A	13-12-1995
		FI 951553 A	02-10-1995
		HU 72048 A	28-03-1996
		JP 7285933 A	31-10-1995
		NO 951252 A	02-10-1995
		NZ 270848 A	26-05-1997
		PL 307951 A	02-10-1995
		US 5654326 A	05-08-1997
		US 5733923 A	31-03-1998
WO 9603383 A	08-02-1996	AU 3145995 A	22-02-1996
		CA 2195570 A	08-02-1996
		CN 1158121 A	27-08-1997
		EP 0772596 A	14-05-1997
		JP 10505584 T	02-06-1998
WO 9640982 A	19-12-1996	US 5707821 A	13-01-1998
		AU 6381496 A	30-12-1996
WO 9517183 A	29-06-1995	US 5478857 A	26-12-1995
		AU 688446 B	12-03-1998
		AU 1402895 A	10-07-1995
		BR 9408407 A	05-08-1997
		CA 2179649 A	29-06-1995
		CN 1142768 A	12-02-1997
		CZ 9601780 A	18-03-1998
		EP 0735870 A	09-10-1996
		FI 962557 A	22-08-1996
		HU 75335 A	28-05-1997
		JP 9507069 T	15-07-1997
		NO 962568 A	09-08-1996
		US 5563164 A	08-10-1996
		ZA 9410041 A	18-06-1996